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OCCUPATIONAL EXPOSURE TO ELECTROMAGNETIC FIELDS, DIETARY AND GENETICS FACTORS AND THE RISK OF BRAIN TUMOURS

A UK CASE-CONTROL STUDY

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Abstract

Nowadays, very little is known of the aetiology of brain tumours in adults and despite all efforts from scientists there is still a limited understanding of this disease. However, previous studies suggest that there is association between some genetic and environmental factors and adults' brain tumours. Risk factors that have been considered to play a role in brain tumours aetiology are exposure to electromagnetic fields (EMF), diet, genetics, ionizing radiation, radio frequency exposure, occupational chemical exposure (pesticides and solvents), head trauma, viruses and it has also been suggested that factors such as allergies or influenza may be important. In this study a detailed literature review obtained for three risk factors; exposure to electromagnetic fields (EMF), diet and genetics.

The current evidence on electromagnetic fields (EMF) as an aetiological factor for brain tumours is inconclusive, existing data suggest weak or no association. We have to consider that exposure to electromagnetic fields is difficult to measure, therefore exposure assessment, particularly in occupation settings, varies from one study to another.

There is currently only limited data for the relation between diet and brain cancer and a number of nutrients have been suggested as potential risk factors. One suggested nutrient is N-nitroso compounds as potential central nervous system (CNS) carcinogens. In addition, there is some evidence of a protective effect of consumption of antioxidants (vitamin C, vitamin E and carotenoids). Other nutrients and foods seem to play a role in brain cancer include zinc and aspartame. According to some studies, the blood-brain barrier in relation with diet might play a role in brain tumour genesis or treatment.

Very little is known for the association of genetics with brain tumours. Many mutated or altered genes, such as p53, Rb1, CDKN2A, p16INK4A, and CDK4, seem to have an involvement in the development of brain tumours, but still the role they play in the formatting of the tumour is not identified. Only about 5% of primary brain tumours are known to be associated with hereditary factors. Common variations in the structure of specific genes are known to be associated with basic cellular metabolic processes such as oxidation, detoxification, DNA stability and repair, and immune functioning. Such genetic polymorphisms may well be associated with the development of brain tumours in the presence or absence of environmental carcinogens.

To better understand the potential risk factors for brain cancer a population based case-control study was conducted in four regions in the UK; Central Scotland, West Yorkshire, West Midlands and Trent was established collecting a wide variety of information including information on occupational sources of electromagnetic fields. This study investigated the link between cumulative electromagnetic field (EMF) exposure that reflected lifetime exposure, rather than electromagnetic field (EMF) exposure from any specific job and glioma, meningioma and acoustic neuroma. Cumulative exposure to electromagnetic fields was determined by generic geometric means assigning to each job coded using Standard Industry Classification (SIC) and Standard Occupation Classification (SOC).

Data were obtained from 970 cases of brain tumours (gliomas n=588; meningiomas n=247; acoustic neuromas n=135) and 1097 controls. For all brain tumour cases, exposures to electromagnetic fields estimated using Standard Industry Classification (SIC) in the 3rd and 4th quartile had a statistically significant decreased risk compared to the first quartile (Q3: OR 0.73, 95% CI 0.55-0.97 and Q4: OR 0.70, 95% CI 0.52-0.94, p for trend 0.019). Similar results were observed with gliomas. No association was found between exposure to electromagnetic fields

(by SIC) and meningiomas or acoustic neuromas. No statistically significant associations were found between exposure to electromagnetic fields by Standard Occupational classification (SOC) coding and brain tumours, gliomas and meningiomas. Exposure to electromagnetic fields estimated using SOC was inversely associated with acoustic neuromas (Q2: adjusted OR 0.53, 95% CI 0.31-0.90, Q3: adjusted OR 0.52, 95% CI 0.29-0.93). Nevertheless, there was no clear trend of risk reduction (p for trend 0.287).

The results in this study do not support the hypothesis that occupational exposure to electromagnetic fields (EMF) is associated with an increased risk of brain cancers. In fact, there is some evidence of a protective effect of electromagnetic fields (EMF) exposure. The healthy worker effect (HWE) may entail differential bias towards the results, as healthy individuals gain employment and remain in industry and ill or disable people not remain employed.

Even though, several epidemiological studies were conducted investigating the risk factors of brain tumours the results are inconsistent. There are still many controversies about the environmental and genetic factors that are important in the aetiology of the disease. For dietary factors, further epidemiological studies need to use data from a big sample size, being obtained from food frequency questionnaires, and try to investigate the role that nutrients/food groups play in brain tumours. More attention must be given in specific nutrients, such the N-nitroso compounds, antioxidants and aspartame. In the analysis confounders, like age, sex, deprivation category, and energy intake, must be adjusted.

The evolution of genetic epidemiological methods we face in the last years increase the amount of information for genetics and investigators need to focus on the data management and analysis of these outputs. Large-scale subjects must be designed in order to investigate candidate genes (p53, Rb1, CDKN2A, p16INK4A, and CDK4)

and genetic polymorphisms and their association with brain tumours. A new approach of studying gene-environmental interaction should be considered with attention, as it might be the direction of the future.

Finally, for electromagnetic fields further studies must be carried out, with detailed complex job-exposure matrixes (JEMs) that will take into account specific job title, description of the tasks each worker is performing, workplace, accurate time of working and even direct measurements of exposure with individual dosimeters. Better classification of jobs must be done and cases with high illness must be included in our sample size, in order to achieve more accurate and precise results.

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Chapter 1
Introduction

1. Introduction

This chapter describes the pathology of brain tumours and their classifications. It then introduces the incidence and mortality of brain tumours. It is followed by a report of epidemiological studies investigating risk factors for brain tumours; in particular it focuses on the potential risk factors of electromagnetic fields (EMF), diet and genetics.

1.1 Pathology of brain tumours

The Central Nervous System (CNS) consists of the brain and the spinal cord. The brain is made up of the cerebrum, the cerebellum and the brain stem (DeAngelis LM 2001). The cerebrum is the largest part of the brain and it is subdivided into four lobes (frontal lobe, parietal lobe, temporal lobe, occipital lobe). The cerebellum located at the back part of the brain, beneath the cerebrum. The brain stem is the portion of the brain, which is connected to the spinal cord and it is composed by the pons, medulla, and midbrain. The central structures of the brain are the thalamus, hypothalamus, and pituitary gland. The ventricles are natural cavities inside the brain filled with cerebrospinal fluid. The meninges, which are membranes, surround the brain and the spinal cord and are responsible for their protection. (www.cancer.net, accessed 28 April 2009). These major areas of the brain are illustrated in figure 1.

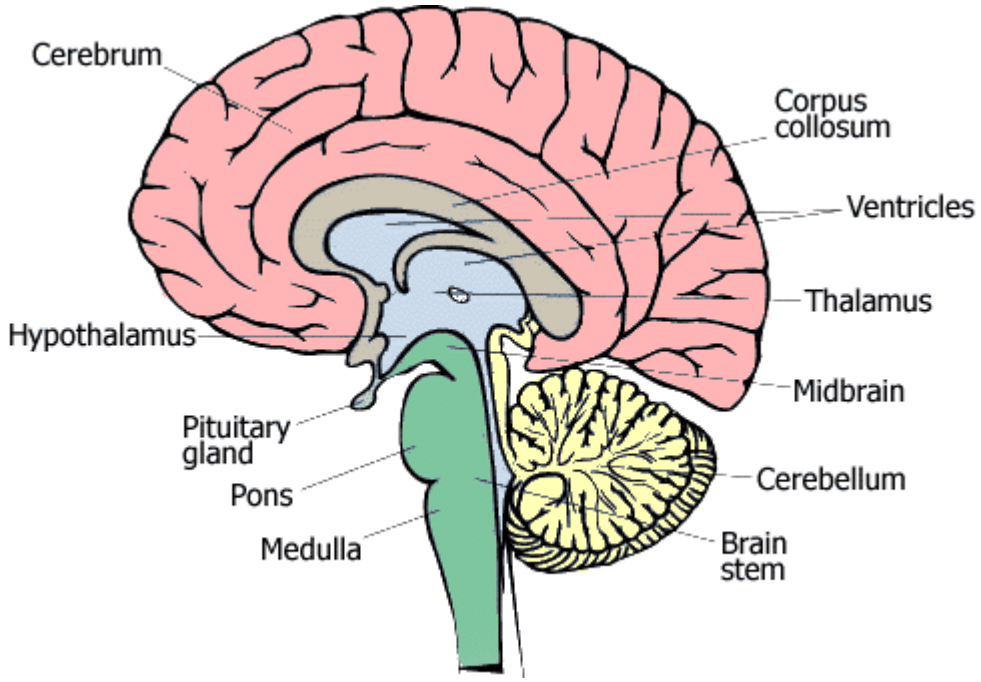


Figure 1. The major areas of the brain

(Picture found in www.medem.com/medlib/article/ZZZYUAM46JC **, accessed 28 April 2009).**

The term brain cancer refers to any of a variety of tumours affecting different brain cell types. An abnormal and uncontrolled growth of cells creates an intracranial mass called as brain tumour (DeAngelis LM. 2001). These cells either normally found in the brain itself: neurons, glial cells (astrocytes, oligodendrocytes, and ependymal cells), lymphatic tissue, blood vessels), in the cranial nerves (myelin producing cells Schwann cells), in the brain envelopes (meninges), skull, pituitary and pineal gland, or spread from cancers primarily located in other organs (metastatic tumours) (DeAngelis LM. 2001). Although they can affect any part of the brain, brain tumours are commonly located in the posterior cranial fossa in children and in the anterior two-thirds of the cerebral hemispheres in adults (DeAngelis LM.2001).

Classification of brain tumours

The brain tumours normally arise from cells present in the brain itself and they are either benign or malignant. In contrast to tumours originating elsewhere in the body, even benign brain tumours tend to transform into malignant forms (DeAngelis LM. 2001). Some types of brain tumours, as meningiomas and lymphomas, do not arise from the brain tissue (DeAngelis LM.2001). Meningiomas arise from the meninges and lymphomas, which is a form of a cancer that begins in the lymphatic system, starts in the brain and can spread to the spinal fluid and eyes (www.cancer.net accessed 28 April 2009).

There is a histologically classification of brain tumours depending on the part of the brain that each tumour arises. The most frequently reported histology is a non-malignant brain tumour, meningioma, which accounts 33.4% of all brain tumours. It is followed by gliomas, brain tumours that arise from glial cells, represent 30% of all brain tumours and 80% of malignant brain tumours. The non-malignant pituitary and nerve sheath tumours account for 12% and 9% of all brain tumours, respectively. Acoustic neuromas account for 60% of all nerve sheath tumours. Lymphomas represent 2.5% of all brain tumours. There are also several types of brain tumours which account for a very small percentage of all brain tumours. All these types represent 12.4% of all brain tumours. The distribution by histology is shown in Figure 2.

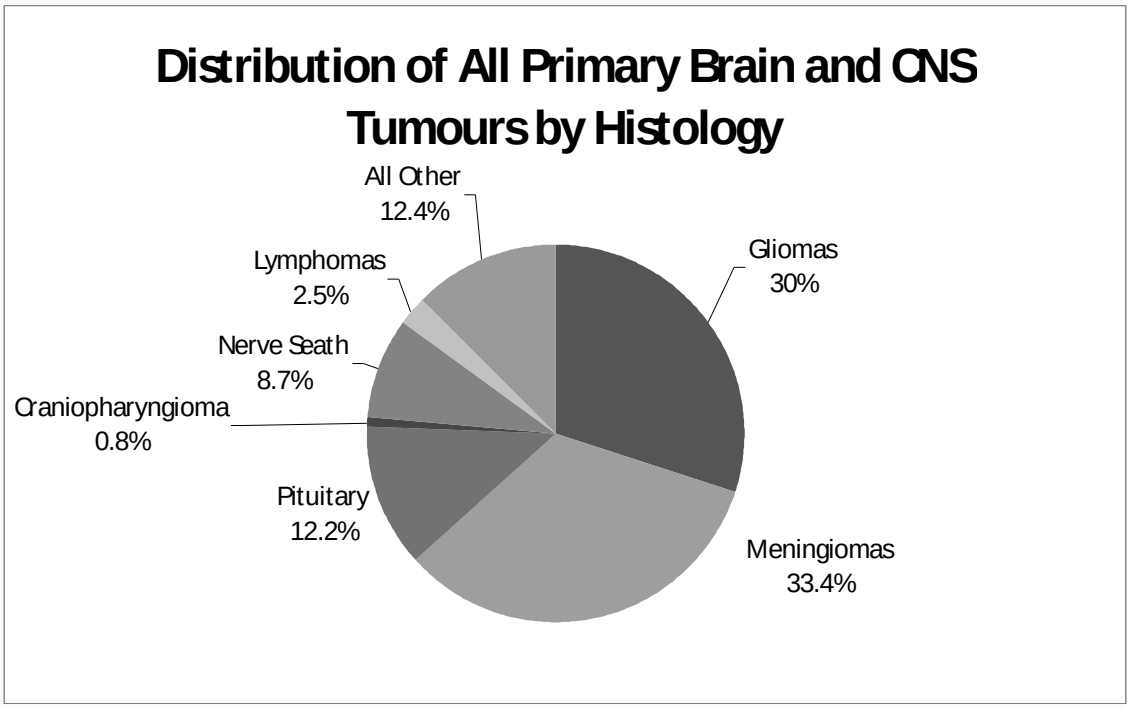


Figure 2. Distribution of brain tumours by histology (CBTRUS Statistical Report 2007-2008).

As mentioned above, gliomas are one of the most primary brain tumours. They are originating from glial, a supportive cell in the brain: astrocytes (astrocytomas) and oligodendrocytes (oligodendrogliomas) (Houben 2006). Astrocytes provide structural support for neurons and maintain electrolyte and neurotransmitter homeostasis in the brain. A role in the physical and chemical integrity of the blood brain barrier is played from astrocytes and ependymal cells (www.cancer.net accessed 28 April 2009). Astrocytoma is one the most common type of glioma and begins in cells called astrocytes in the cerebrum or the cerebellum (DeAngelis LM. 2001). There are three malignancy grades of astrocytomas, according to the World Health Organisation (WHO) (Kleihues et al 2000), grade II astrocytoma, grade III anaplastic astrocytoma and grade IV glioblastoma multiforme, based on several pathological criteria such as cellularity, nuclear atypia, mitosis, microvascular

proliferation and necrosis. Astrocytomas account for a 7.4% of all brain tumours and for a 22.6% of all gliomas (CBTRUS Statistical Report 2007-2008).

Glioblastoma is a malignant astrocytoma that contains areas of dead tumour cells. Approximately 50% of astrocytomas are glioblastomas (Kleihues et al 2000). Glioblastomas typically contain more than one cell type. While one cell type may die off in response to a particular treatment, the other cell types may continue to multiply. This characteristic makes glioblastomas very difficult to treat (www.cancer.net accessed 28 April 2009). Glioblastomas represent the 17.6% of all brain tumours and the 54% of all gliomas (CBTRUS Statistical Report 2007-2008).

Oligondedroglioma is a tumour that develops from cells called oligodendrocytes. Oligodendrocytes produce and maintain myelin in the central nervous system and ependymal cells form the endothelium that lines the ventricles of the brain and the central canal of the spinal cord (DeAngelis LM. 2001). In oligodendroglioma only two malignancy grades are distinguished, WHO grade II oligodendrogliomas and grade III anaplastic oligodendrogliomas (Kleihues et al 2000). Oligodendrogliomas represent 2.1% of all brain tumours and 6.6% of all gliomas (CBTRUS Statistical Report 2007-2008). There are also mixed forms, with both an astrocytic and an oligodendroglial cell component. These are called mixed gliomas or oligoastrocytomas. Additionally, mixed glio-neuronal tumours (tumours displaying a neuronal, as well as a glial component, e.g. gangliogliomas, disembryoplastic neuroepithelial tumours) and tumours originating from neuronal cells (e.g. gangliocytoma, central gangliocytoma) can also be encountered (Houben 2006). The distribution of all gliomas by histology subtypes is illustrated in figure 3.

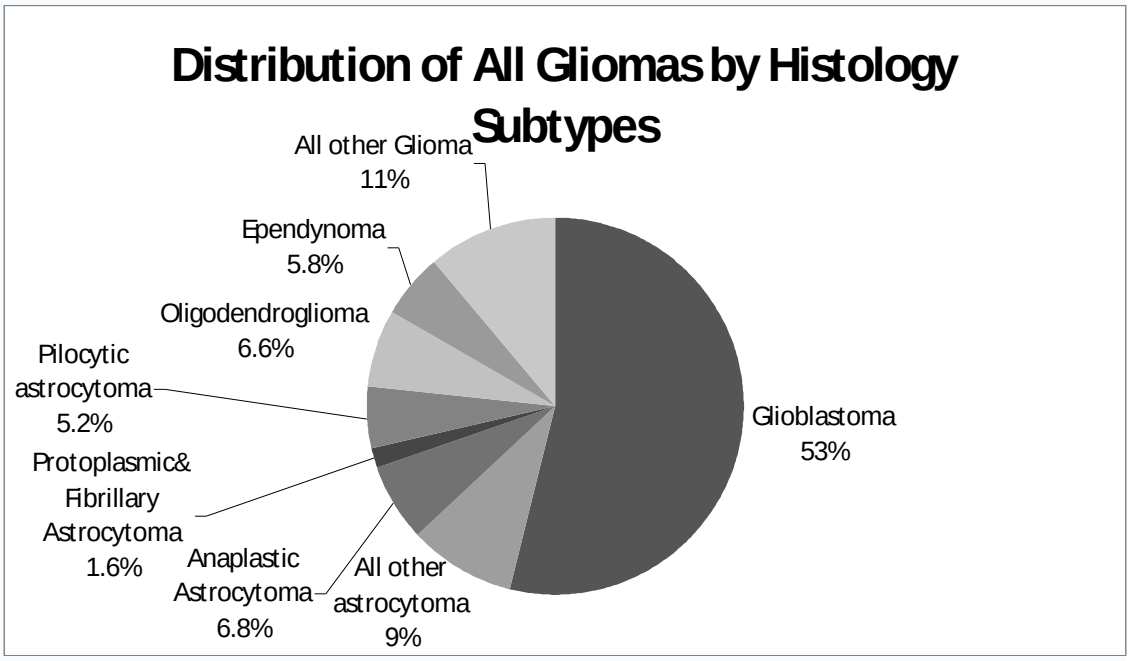


Figure 3. Distribution of all gliomas by histology subtypes (CBTRUS Statistical Report 2007-2008).

True benign intracranial tumours arise mainly from the meninges (meningiomas; about 90% are benign), pituitary gland (pituitary adenomas) and the myelin sheath of cranial nerves (neuromas or Schwanomas, e.g. acoustic neuroma) (DeAngelis LM. 2001). Meningiomas constitute approximately 33.4% of brain tumours and normally form on the surface of the brain. They can cause significant symptoms if they grow and press on the brain or spinal cord or invade into the brain tissue. The majority of meningiomas grow slowly and characterised by the loss of the chromosome 22q (DeAngelis LM. 2001). Pituitary gland tumours are not brain tumours, as this gland sits beneath and separate from the brain, but can cause serious symptoms in other organs or systems. Generally, they are benign but sometimes can show malignant behaviour. A rare type of tumour is the acoustic neuroma, which begins in the vestibular nerve (a nerve in the inner ear that helps control balance), and is normally benign (www.cancer.net, accessed 28 April 2009).

Other varieties of primary brain tumours include: primitive neuroectodermal tumours (PNET, e.g. medulloblastoma, medulloepithelioma, neuroblastoma, retinoblastoma, and ependymoblastoma), tumours of the pineal parenchyma (e.g. pineocytoma, pineoblastoma), ependymal cell tumours, choroid plexus tumours, neuroepithelial tumours of uncertain origin (e.g. gliomatosis cerebri, astroblastoma), etc. (DeAngelis LM. 2001, Kleihues et al 2000).

Symptoms and Diagnosis

The symptoms brain tumours cause are either focal or generalised neurogical (Houben 2006). Focal symptoms are normally hemiparesis and aphasia and reflect the intracranial location of the tumour. The generalised symptoms that occur, such as headache, nausea vomiting and visual complaints, are the result of the increased intracranial pressure (DeAngelis LM. 2001).

The diagnosis of brain tumour relies on modern neuroimaging techniques. Therefore, the cranial magnetic resonance imaging (MRI) with gadolinium enhancement is the test which can establish easily the diagnosis (DeAngelis LM. 2001). If we want to obtain tissue for histopathological diagnosis, after MRI, a biopsy or surgical decompression must be followed (Houben 2006).

1.2 Epidemiology of brain tumours

Incidence and mortality:

Nowadays, the incidence of brain tumours appears to be on the rise, especially in developed countries. Improved diagnostic techniques attempt to provide the reason for these large scale changes. According to the statistical report of the Central Brain Tumour Registry of the United States (CBTRUS) and the International Agency for Research on Cancer (IARC) the worldwide incidence rate of primary malignant brain tumors, age-adjusted using the world standard population, is 3.7 per 100 000 persons-years in males and 2.6 per 100 000 persons-years in females. The incidence rates are higher in more developed countries (males: 5.8 per 100 000 persons-years, females: 4.1 per 100 000 persons-years) than in less developed countries (males: 3.0 per 100 000 persons-years, females: 2.1 per 100 000 persons-years). (CBTRUS Statistical Report 2007-2008). Official crude incidence for brain tumours in Great Britain is approximately 7 per 100,000, or 4000 new cases per year. In Great Britain, brain tumours are the 8th commonest malignancy in adults under 65 and in adults under 45s the fourth most common (Black et al 1993, Sharp et al 1993), emphasizing the importance in the working population. In Scotland the 10.7% of all registered cancer deaths in under-45s were attributed to brain tumours (Grant et al 1996). An increase in incidence has been observed in parts of the UK (Sharp et al 1993) and elsewhere in the world, including Western Europe and the US (Polednak 1991, Davis et al 1990). Most studies suggest that the rise is not artefactual, even though advances in diagnostic techniques may account for a proportion of the increase, particularly in the elderly.

In 2007, in the UK there were 3,611 deaths from brain and other central nervous system cancers, which accounted for just over 2% of all cancer deaths (Office of National Statistics, Mortality Statistics, England and Wales 2007, accessed February 2009). The mortality rate in Great Britain is 5.0 per 100 000 persons-

years. The mortality rate is higher among males (6.1 per 100 000 males-years) than among females (4.0 per 100 000 females-years) (The Office of National Statistics, Mortality Statistics, England and Wales 2007, accessed February 2009). A previous study of cancer mortality in England and Wales identified Central Nervous System (CNS) tumours as one of the cancers showing a remarkable rise in mortality, as the rates rose more than sixfold between 1950 and 1989 (Coggon & Inskip 1994).

1.3 Risk factors of brain tumours

1.3.1 Electro Magnetic Fields

The association of brain tumours and exposure to electromagnetic fields (EMF) has been a major concern and several studies were conducted to examine the role that the exposure to electromagnetic fields might play in this disease.

Introduction to electromagnetic fields

Magnetic and electric fields are both associated to electric current flow and the term electromagnetic fields (EMF) is commonly referred to both (WHO -World Health Organization, 2006). Magnetic fields (MF) arise from electric current flows and Electric fields (EF) from voltage and exist even when there is no current flow (Marcílio et al, 2009). Electromagnetic fields generated by different sources, either natural (solar radiation and ultraviolet light) or human-made (radiowaves and electric power) (WHO -World Health Organization, 2006). The strength of the Electric field is measured in Volts per metre (V/m) and the strength of the Magnetic field in Amperes per metre (A/m). Electromagnetic fields (EMF) investigators use a related measure, flux density (in microtesla (μT) or millitesla (mT) instead (Marcílio et al, 2009). The frequency of electromagnetic fields (EMF) measured in Hertz (Hz)

and size of waves. Direct current or static fields have 0 Hz frequency, which is the lower end of the frequency spectrum. Ionizing radiations –X-rays, Gama rays, and ultraviolet light - with frequency above 10^{16} Hz are the upper end. Low frequency fields occupy the range from 3 to 3,000 Hz, with long wavelength. Extremely low frequency electromagnetic fields are ranging between 50 Hz and 60Hz (CEA - Canadian Electricity Association. 2006).

Biological Mechanisms

The only established mechanism of action of extremely low frequency magnetic fields (ELF MF) is the interaction of these fields with tissues of the human body by inducing weak electric currents in them (Marcílio et al, 2009). These fields are also known as "non-ionizing radiations" and they cannot break any chemical bonds (Ahlbom et al 2003). The nervous system works by electric stimulation and it seems to be susceptible to the effects of the magnetic fields (WHO –World Health Organization, 2007). Even though the electric currents induced by extremely low frequency magnetic fields (ELF MF) are weaker than the ones physiologically occur in the human body, there are evidence suggesting that these currents may increase the functional electric activity in the central nervous system (CNS) (Saunders et al 2007, WHO –World Health Organization, 2007). From studies which conducted there is no evidence that extremely low frequency electromagnetic fields have enough energy to break DNA bonds or cause a carcinogenic process (Poole et al. 1996, Ahlbom et al. 2001). Only exposure equal or above 100 μT seems to have an adverse health effect (Kheifets et al. 2005). Even if experimental studies have not been able to establish any biological mechanism explaining the interaction of extremely low frequency magnetic fields and the human body, there must be one since there is evidence from epidemiological studies showing that this exposure may have an adverse health effect (WHO –World Health Organization, 2007).

Occupational exposure assessment

The major problem that epidemiological studies faced attempting to investigate the association between brain tumours and exposure to electromagnetic fields (EMF) is the assessment and quantification of the exposure (Ahlbom et al 2001, Feychting et al 2005, WHO –World Health Organization 2007). This difficulty calculating the exposure is due to the fact that we have not indentified a specific method to estimate the accurate exposure to electromagnetic fields. Exposure to electromagnetic fields is complex, as it is generated from several sources, and still it is not found an established methodology to add-up these exposures in one total exposure (Ahlbom et al 2001, WHO –World Health Organization 2007). In addition, difficulties arise for the definition of the induction period to electromagnetic fields (Ahlbom et al 2001). All these are obstacles to establish relevant parameters for the quantification of the exposure to electromagnetic fields and make more difficult the assessment of the effects of this exposure to brain tumours (Ahlbom et al 2001, WHO –World Health Organization 2007).

Most of the studies conducted focus in the occupational exposure assessment, as electromagnetic fields intensity in certain jobs, for instance, can reach much higher levels than in residential exposure (Ahlbom et al 2001). Estimation of the occupational exposure can be obtained with job categories calendars or more complex matrices of exposure (Marcílio et al 2009). Another way is a detailed assessment of a sample of workers through personal dosimeters (Ahlbom et al 2001).

Epidemiological studies

Studies have examined the possible association between brain tumours and exposure to extremely low frequency magnetic fields (ELF MF). Nichols and Sorahan (2005), in their cohort study of UK electricity generation and transmission workers, found significant excesses of deaths from brain cancer in male workers from non-operational locations (Observed-Obs: 55, Expected-Exp: 36.0, Standardized Mortality Ratios-SMR: 153), but previous studies in the UK found no association between increased risk of brain tumour and exposure to extremely low frequency magnetic fields (ELF MF) in the power generation and supply industry (Harrington et al., 1997; Sorahan et al., 2001). In 2002, IARC reviewed the evidence of carcinogenicity of extremely low frequency electric and magnetic fields (ELF MF) and concluded that ELF MF exposure are possibly carcinogenic to humans, although this was predominantly based on evidence from residential exposure and childhood leukaemia studies. This evidence suggests that residential exposure to extremely low frequency electromagnetic fields might play a role in the carcinogenesis of childhood leukaemia (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2002).

One of the hypotheses of the UK Adults Brain Tumour Study (UKABTS) is to evaluate the association between exposure to extremely low frequency magnetic fields (ELF MF) and brain tumours risk. This study found evidence that electrical work amongst males was associated with an increased risk of developing glioma (Odds Ratio 1.4, 95% CI 0.9-2.0) (van Tongeren et al., 2007). Although increase risk is not statistically significant in this study it shows that investigations for finding an association between electromagnetic fields and brain tumours are in the right direction. The results were in keeping with other studies (e.g. Preston-Martin et al., 1993; Loomis and Savitz, 1998; Thomas et al., 1987; Zheng et al 2001). The strongest risks were shown in Preston-Martin et al studies investigating

exposure to electromagnetic fields and the risk of brain tumours among electricians (OR 4.6, 95% CI 1.7-12.2) and electrical engineers (OR 8.2, 95% CI 20-34.7), even though increase risks are not statistically significant (Preston-Martin et al 1993). Loomis and Savitz study found that increasing cumulative magnetic field exposure was associated with increasing mortality in brain tumours patients, with rate ratios (RR): 1.3-3.4 for the most exposed workers (Loomis and Savitz 1998). A case control study of brain tumours and occupational risk factors in northern New Jersey shown elevated relative risk (RR) for all brain tumours among men exposed to microwave and radiofrequency (MW/RF) radiation (RR 1.6; 95% CI 1.0-2.4) and was significantly elevated among men exposed for 20 or more years. Also, this study showed an increase risk of developing brain tumour among electrical or electronic workers (RR = 2.3; 95% Cl = 1.3-4.2) (Thomas et al 1987). In Zheng et al case control study a significantly increase risk was obtained for employment of more than 10 years in occupations or industries with electric or electronic equipment (Zheng et al 2001).

Little is known about occupational extremely low frequency magnetic fields (ELF MF) levels outside this industry sector in the UK, even though in the power generating and distributing industry there is relatively abundance of ELF MF exposure information (Merchant et al., 1994; Renew et al, 2003). The study team therefore designed a study within the UKABTS project to collect extremely low frequency magnetic fields (ELF MF) measurements on a subset of the UKABTS participants (van Tongeren et al 2004, Mee et al 2006). Information on occupation, tasks and use of equipment was obtained during interviews using Computer Assisted Personal Interview (CAPI) software (van Tongeren et al 2004). Additional data were collected with Emdex II magnetic fields meters (Enertech Consultants Ltd, California, USA). Individuals who agreed to participate were wearing the meters at the waist and left them at the bedside overnight (Mee et al 2006). Exposure data were downloaded using EMCALC software and time weighted

average (TWA), standard deviation (SD), geometric mean (GM) and other metrics were computed (van Tongeren et al 2004). Results from a feasibility study supported that it is possible to collect occupational exposure data from participants at a moderate cost (van Tongeren et al 2004). For example, welding and working near high voltage cables were associated with an elevated level of exposure. There were some suggestions that extremely low frequency magnetic fields (ELF MF) exposure during other tasks, such as high current wires, power stations, motors and electrical transport, were also increased, although this was not statistically significant, as compared to welding and working near high voltage cables (van Tongeren et al., 2004). In an article by Mee et al (2006) there is a suggestion that using information on tasks and working environment could improve any exposure models (Mee et al 2006).

1.3.2 Diet

Limited data exist regarding associations between diet and brain tumours. In view of the few studies done, we cannot say for certain which nutrients are responsible for an increased or reduced risk; however an association between brain tumours and diet is suggested. There are several nutrients or food groups that are assumed to play a role in brain tumours. N-nitroso, antioxidants (fruit, vegetables, zinc etc) and aspartame are the most important.

N-nitroso compounds:

One of the hypotheses that have been previously formulated is that N-nitroso compound (NOC) synthesis is involved in the pathogenesis of brain tumours (Burch et al 1987, Ahlbom et al 1986, Tedeshi-Blok et al 2006, Preston- Martin and Mack 1991, Inskip et al 1995, Giles 1997, Pereira and Koifman 2001), even though some

studies failed to demonstrate an association (Steindorf et al 1994, Ryan et al 1992, Lubin et al 2000, Chen et al 2002).

N-nitroso compounds and, specifically, certain nitrosamides and nitrosamines result from reactions in the stomach involving nitrites, amides and amines present in the diet (Inskip et al 1995). High levels of nitrite can be found in bacon and other cured meats, fish, cheese, baked goods and cereals (Howe et al 1986, Inskip et al 1995). Another source of nitrite is the drinking water (Walker et al 1975, MØller et al 1989). Also vegetables contain nitrites, but due to the fact that vegetables also contain Vitamin C and E the nitrosation process is blocked (Inskip et al 1995). There is a lack of knowledge, even though, for the biological mechanism that occurs so the N-nitroso compounds reach the brain. The nitrosation process can occur outside the stomach too, through cell pathways involving endothelial cells and some neurons (Leaf et al 1989). Certain alkylating agents, such as ethyl and methyl nitrosurea, are able to cross the blood-brain barrier and due to their mutagenic potential can play a role in the carcinogenic process (McKinney P A 2004).

The produced results from the epidemiological studies investigating the association of N-nitroso compounds with brain tumours are mixed and inconclusive. A study that had taken place in United States showed that women whose diets were rich in nitrites had an increased risk of having a child who would later develop brain tumours (Preston-Martin et al 1996). Burch et al (1987) reported significantly elevated risks for salted, pickled, and smoked fish, but not for processed meats (Burch et al 1987). The intake of processed meat, such as cooked ham, processed pork, and fried bacon, was significantly associated with an increased risk of glioma (Boeing et al 1993). In a case-control study carried out in Melbourne increased odds ratio (OR) were observed in males who consumed high levels of bacon, corned meats, apples, melons and oil (Giles et al 1994). Nitrate levels in drinking

water have been investigated and produced increase risk of developing brain tumours (Burch et al 1987), although a study in Germany failed to demonstrate an association (Steindorf et al 1994). An international case-control study by Terry et al (2009) found no association for cured meat, but non- cured meat seem to be associated with a modest increase glioma risk (OR, 1.3; 95% CI, 1.0–1.7, p for trend = 0.01) (Terry et al 2009).

No association was found with nitrosamines or high-nitrate vegetables, nitrate and nitrite in another study by Chen et al (2002) in eastern Nebraska. A study by Lubin et al (2000) in Israel showed no increased risk as a result of consumption of food containing nitrates or nitrites. Preliminary results from individual centres do not suggest a significant role for exposure to N-nitroso compounds (Ryan et al 1992). Dietary sources are currently being investigated in a multi-centre case-control study co-ordinated by the International Agency for Research on Cancer (IARC).

Antioxidants (fruit, vegetables, vitamins, zinc)

The "antioxidant hypothesis" is another formulated hypothesis suggesting that antioxidant nutrients such as vitamin C, vitamin E, carotenoids and zinc are involved with an inverse disease association (Stanner et al 2004, Chen et al 2002, Hu et al 1999, Pereira and Koifman 2001, Preston-Martin 1989, Vallee 1993, Ho 2002). A study by Lubin et al (2000) didn't show any protective effect attributed to consumption of fruits and vegetables.

There is a suggestion that antioxidant nutrients such as vitamins C and E and carotenoids are protective, as they reduce oxidative damage (Bondy et al 1991, Stanner et al 2004). Also, vitamins block the nitrosation process and this is might be a reason of being protective (Inskip et al 1995). In animal studies, Vitamin E seems to play a role for the good function of brain cells, as vitamin E deficiency is linked with increased formation of oxygen radicals (LeBel et al 1989). Carotenoids

modulate DNA repair and have antioxidant (Astley et al 2004] and anti-inflammatory action (Quasim et al 2003, Chew 2004).

Some results of epidemiological studies are compatible with the antioxidant hypothesis. An international case-control study by Terry et al (2009) found inverse association between some vegetable groups, especially yellow-orange vegetables, and glioma risk. Another study by Chen et al (2002) in eastern Nebraska observed inverse disease associations for intake of dark yellow vegetables (OR: 0.6, $p_{trend:}$ 0.03) and beans (OR: 0.4, $p_{trend:}$ 0.0003),, pro-vitamin A carotenoids (OR: 0.5, $p_{trend:}$ 0.005), a-carotene (OR: 0.5, $p_{trend:}$ 0.01), dietary fibre (OR 0.6, $p_{trend:}$ 0.048) and fibre from beans (OR: 0.5, $p_{trend:}$ 0.0002). However, no association was found with vitamin C and E, dietary fibre from grain products or fibre from fruit and vegetables. A study conducted in United states showed that women who took vitamins (A, C, E) had an inversely related risk of having a child with a brain tumour (OR: 0.54; CI 0.39-0.75) (Preston-Martin et al 1996). A case-control study by Hu et al (1999) in Northeast China showed that consumption of fresh vegetables (OR 0.29), specifically Chinese cabbage and onion, fruit (OR 0.15), fresh fish (OR 0.38) and poultry (OR 0.16), was inversely related to the risk of brain tumour. A protective effect was also seen for vitamin E intake, calcium, beta-carotene and vitamin C (Hu et al 1999).A study by Lubin et al (2000) in Israel showed no protective effect attributed to consumption of fruits and vegetables.

Zinc, due to its antioxidant properties, can be protective against brain tumours development (Blowers et al 1997). Zinc is important for DNA replication, protein synthesis and metabolism (Vallee 1993), oxidative stress protection (Stehbens 2003) and DNA repair (Bourre 2006). In animal studies, zinc found to play a role for the good function of neurons and glial cells (Bediz et al 2006, Warming et al 2006, Colvin et al 2000, Takeda et al 1994). In a case-control study conducted in Trent, West Midlands, West Yorkshire and central Scotland a statistically significant

risk reduction for meningioma was observed only in the 3rd quartile of dietary zinc (Zn) intake (OR 0.62, 95% CI 0.39-0.99, p=0.048) and was not significant after also adjusting for intake of other elements. Overall there was no significant effect of Zn intake therefore the specific hypothesis on a protective effect of increased compared with low levels of dietary Zn against glioma or meningioma formation is not supported. (Dimitropoulou et al 2007).My involvement in this study was the data entering and some literature review.

Aspartame:

The low-calorie sweetener aspartame has been commonly used in a number of food products for over 15 years. It has been suggested, principally from laboratory experiments, that it is involved in the aetiology of some brain tumours (Janssen et al 1998). In addition, it has have suggested that it may be one of the contributing factors in the increasing rate of central nervous system tumours in Western societies (Olney et al 1996). The way in which aspartame influences the brain tumour risk is unclear; it is possible that alteration of the blood-brain barrier occurs or that once ingested, aspartame becomes nitrosated, and thereby may be carcinogenic (Shephard et al 1993, Yokogoshi et al 1984). The possibility that aspartame may be a cause of brain cancer in humans was implied in the Gurney et al (1997) study, but no relation was found.

Diet literature review summary and potential areas of bias

In summary, results from epidemiological studies investigating the role of diet in brain tumours are inconsistent. Many hypotheses were formulated in relation to brain cancer and a range of nutrients and foods have been suggested to be associated with the disease. Several studies support some of the existing dietary hypotheses, suggesting that diet might be a risk factor of brain tumours (Wrensch, 2002).

One of the hypotheses that have been previously formulated is that N-nitroso compound (NOC) synthesis has an involvement in the formation of brain tumours (Burch et al 1987, Ahlbom et al 1986, Tedeshi-Blok et al 2006, Preston- Martin and Mack 1991, Inskip et al 1995, Giles 1997, Pereira and Koifman 2001), even though some studies failed to support an association (Steindorf et al 1994, Ryan et al 1992, Lubin et al 2000, Chen et al 2002). The "antioxidant hypothesis" is another formulated hypothesis suggesting that antioxidant nutrients such as vitamin C, vitamin E and carotenoids have an inverse association with the disease (Stanner et al 2003, Chen et al 2002, Hu et al 1999, Pereira and Koifman 2001, Preston-Martin 1989). A study by Lubin et al (2000) didn't show that consumption of fruit and vegetables has any protective effect. Besides these main hypotheses, some other nutrients, such as zinc and aspartame, suggested to play a role in brain tumours according to other studies (Shephard et al 1993, Yokogoshi et al 1984, Blowers et al 1997, Bediz et al 2006, Warming et al 2006).

Diet data can be obtained with Food Frequency Questionnaires (FFQ) and average daily nutrient consumption can be calculated by multiplying the daily consumption frequency of each food item by the content of the examined nutrient in the respective food item obtained from food composition tables (Holland et al 1991, Lophatananon 2004).

Brain tumour studies have some problems due to the heterogeneity in morphology and malignancy grade of the brain tumours examined. The food frequency questionnaire (FFQ) method consider to be a good one, as it is cheap, easy to administer, and provides quick intake estimates (Willett, 1998). The frequency question that is made in the food frequency questionnaire usually is combined with a specific 'medium portion' size and this can confuse the subjects and cause a recall bias (Pietinen, 1988). A misclassification can be occurred as average portion sizes are being used for the estimation of the nutrient intake. This might lead to a

loss of power of the study (Friedenreich et al. 1993). However, several studies have found that consumption frequency is correlated with portion size (Jain et al, 1996).

Subjects normally were asked to report their dietary habits during the two years prior to diagnosis, as this period is more likely to overlap with the period of brain tumor development (aetiologically relevant period) (Friedenreich et al. 1993). The latency period of the disease is, generally, undefined (Wrensch, 2002). As brain tumour patients normally suffer from loss of memory and concentration, they might response based on current dietary habits even if the question is for previous diet (Nelson 2000, Thompson 1994).

A common problem for many population-based studies is the low control participation and it might introduce selection bias amongst controls (Willett, 1998). A potential source of bias can be the differential participation of controls that have healthy diet habits, as they may have better nutritional regimes than the general population (Friedenreich et al. 1993). Deprivation category is adjusted for in the analysis, although the bias cannot be fully removed. Other confounders, such as age, sex, region, are necessary to be adjusted for in the analysis too. Energy intake maybe an important disease predictor, therefore it is necessary to be included in the regression model together with the nutrient energy-adjusted term (Willett 1998).

In the UK Adults Brain Tumour Study (UKABTS) a rich diet dataset is available for further investigations.

1.3.3 Genetic factors

Genetics of brain tumour

Several studies were conducted investigating whether genetic changes or metabolic susceptibility genes have a role in brain tumours; the majority of the evidence supports the hypothesis that genetic changes can be assumed to be a risk factor for brain tumours but it is clear that metabolic susceptibility genes play little, if any, role in brain cancer (Seymour, 2001).

Brain tumours, as well as other cancers, result from a multiple changes in cell's DNA leading to tumour formation (Houben 2006). It is believed that altered (mutated) or missing genes enable cancer to develop (Jones et al 2002). Some of these mutations are constitutional and can be transmitted from one generation to the next (Houben 2006).

The genes that are involved in the development of brain tumours can be classified into three groups: proto-oncogenes, tumour suppressor genes, and DNA repair genes (Knudson AG. 2002). The proto-oncogenes transform into oncogenes with an activating mutation in one or both gene copies and stimulate uncontrolled cell growth. An inactivating mutation in both copies of the tumour suppressor genes inhibits the growth of cells (Knudson AG. 1971). Prevention of brain tumour formation is caused by DNA repair genes, which repair DNA damage, occur by mutagenic agents (Houben 2006).

Candidates mutated or altered genes

Most genetic investigations of brain tumours were focused on mutation and gene alterations (loss of function of tumour suppressor genes or overexpression of

proto-oncogenes). It is believed that altered (mutated) or missing genes enable cancer to develop (Jones et al 2002). The loss of 17p (including p53), 9p, 10, 11p, 13q, 19 and 22q are some of the alterations that cause changes in the expression of several genes, such as phosphatase and tensin homolog (PTEN), deleted-in-colon carcinoma (DCC), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), mouse double minute 2 (MDM2), glioma-associated oncogene homolog (GLI), cyclic AMP-dependent kinase number 2 A/B (CDKN2A/B), cyclin-dependent kinase 4 and 6 (CDK4/6) etc (Kleihues et al 1999).

Epidemiological studies that conducted found that altered genes involved in brain tumours, but couldn't explain the role these genes play in brain tumours formation. The most common altered gene that seems to involve is p53. In gliomas, p53 is the most frequently altered gene, involved in the early phase of glioma development (Harada et al 2003). According to Bian et al (2000), the frequency of mutant p53 protein expression was higher in grade 2-4 astrocytomas than in grade 1 in 97 cases. These cases were investigated with immunohistochemistry and image analyzer to detect oncoproteins and it was concluded that p53 over-expression is involved in astrocytomas. There exist data (Khodarev et al 2004) which suggest that blockade of p53 function may alter the relationship between tumour cells and endothelial cells, such that the latter exhibit an increase in radio-sensitivity. According to Kutler et al (2003), the squamous cell carcinomas seen in Fanconi anaemia patients are probably caused by the inactivation of p53 by HPV-associated oncoprotein rather than by direct mutagenesis.

Some other altered genes which have an involvement in carcinogenesis of brain tumour are TP53 tumour suppressor gene, PTEN, CDK4, MDM2, CDKN2A tumour suppressor gene and p14ARF. In the Kraus et al (2002) study, mutations of the TP53 tumour suppressor gene were found in the 8% of the supra-tentorial primitive neuroectodermal tumours (sPNETs) and in the 33% of the glioblastoma

multiforme (GBM), but none of sPNETs and GBM showed allelic losses on chromosome arm 17p. PTEN mutations were detected in the 8% of sPNETs and 17% of GBMs but none was carrying homozygous deletion involving the CDKN2A tumour suppressor gene. The CDK4 or MDM2 proto-oncogenes were detected. These results indicate that GBMs differ from sPNETs by a higher incidence of allelic losses on 17p and TP53 mutations. PTN immunoreactivity was increased in low-grade astrocytomas compared to normal brain (Ulbricht et al 2003). Although it is a secreted growth factor, it appears to serve as a substrate for migrating tumour cells. Another study is suggesting that in cell cycle pathways, deregulation of G1-S transition control is one of the important mechanisms in the development of astrocytic gliomas through inactivation of the p53 pathway. Abnormalities exist either by mutation/homozygous deletion of RB1 or CDKN2A, p16INK4A or amplification of CDK4 (Ichimura et al 2000).

One example of growth factor-regulated signalling pathways is that of HIF-1, which initiates the transcription of a number of genes, including those encoding vascular endothelial growth factor and its receptors. Also, an epidermal growth factor receptor (EGFR) gene is amplified or mutated in 30-50% of human glioblastoma multiforme (Holland 2000). P53-mediated apoptosis is involved in glioblastomas, and Apaf-1 is a major effect. The p53 gene mutation and EGFR gene amplification were found in 13 cases (39%) and 8 cases (24%), respectively, and these gene alterations were inversely correlated (Watanabe et al 2003).

There are two proposed genetic pathways that link clinical findings with molecular genetic evidence. In the first pathway, it is believed that low grade astrocytomas can be developed from a p53 mutation, plus PDGF mutation, PDGFR overexpression and a loss of gene in 22p. From there, a retinoblastoma (Rb1) alteration, plus a loss of genes on 19q and 9p are responsible for the formation of anaplastic astrocytomas and finally, a loss of gene on 10q with an amplification of

PDGFR lead to a secondary glioblastoma (Lang et al 1994, Louis et al 1993). In the second hypothetical pathway, it is thought that EGFR and MDM2 amplification or overexpression, plus p16 deletion, loss of genes on 10p and alteration in Rb1 and PTEN can lead to a formation of primary glioblastomas (Watanabe et al 1996).

Even though, all these mutated or altered genes have been suggested to have an involvement in brain tumours, there is no clear explanation why these healthy cells transform into tumour ones. The genetic aetiology of brain tumours remains puzzling and further investigations need to be conducted in order to explain whether gene alterations and mutations play a role in brain tumours formation.

Hereditary factors

Only about 5% of primary brain tumours are known to be associated with hereditary factors (Bondy et al 1991, Wrensch et al 1997, Narod et al 1991). In particular, those with Li-Fraumeni syndrome (LFS) (Li et al 1988), tuberous sclerosis (Shepherd et al 1991), neurofibromatosis (Kinzler et al 1993), Turcot syndrome (Turcot et al 1959) and Gorlin syndrome (Hahn et al 1996, Corlin et al 1995), have a higher incidence of brain tumours than the general population.
The hereditary brain tumour syndromes and the genes responsible for these conditions are summarised in the follow table (table 3).

Table 1. Hereditary brain tumour syndromes and corresponding tumour types (modified from Kleihues and Cavanee 2000 and Current Diagnosis & Treatment in Neurology book 2006)

Syndromes	Mutation	Tumour type
Gardner syndrome	APC	Colonic polyps, astrocytomas
Li-Fraumeni syndrome	P53 Mutation	Solid systemic cancers, astrocytomas ,glioblastomas multiforme
Multiple endocrine Neoplasia type (MEN) 1	Chromosome 11	Pituitary adenomas
Neurofibromatosis (NF) types 1 and 2	Chromosome 17 NF1 Chromosome 22 NF2	Neurofibromas, acoustic neuromas, meningiomas, astrocytomas
Gorlin	Chromosome 9 PTCH	Medulloblastomas, astrocytomas, ependynomas, glioblastomas multiforme
Melanoma-astrocytoma	CDKN2A	Astrocytomas, meningiomas, acoustic neuromas
Turcot syndrome	Chromosome 5 APC	Colonic polyps, astrocytomas, medulloblastomas
Von-Hippel Lindau syndrome	Chromosome 3	Infratentorial and spinal cord hemangioblastomas

Genetic polymorphisms and the risk of brain tumour

Genes with multiple alleles are called polymorphisms and seems to play a little role in brain tumours development (Seymour 2001). These genes are known to be associated with different processes such as oxidation, detoxification, DNA stability and repair, and immune functioning (Houben 2006).

The best studied polymorphisms are those in the carcinogen-metabolising enzymes glutathione S-transferase (GST). The genes encoding GSTM1, GSTT1, and GSTP1 are polymorphic (GSTM1 wildtype/null, GSTT1 wildtype/null, GSTP1 Ile105V and GSTP1 Ala114Val) (Eaton et al 1999). A statistically significant association between GSTT1 null genotype and the risk of astrocytomas was reported in a previous study (astrocytomas: OR 2.09, 95% CI 1.28-3.39 and High Grade astrocytomas: OR 2.36, 95% CI 1.41-3.94) (Elexpuru-Camiruaga et al, 1995). Another case-control study found no association between GSTT1 null and the risk of developing brain tumour (Trizna et al 1998). Evidence exists for an association between GSTP1 Ile105V genotype and glioma (OR 1.8, 95% CI 1.2-2.7) (De Roos et al 2003).

CYP genes are also involved in carcinogen metabolism and detoxification. Even though, no association between CYP2D6 and gliomas is confirmed in a population-based case-control study (Kelsey et al 1997), a hospital-based case-control study showed that poor metabolising variants of CYP2D6 were associated with gliomas (OR 4.17, 95% CI 1.57-11.09) (Elexpuru-Camiruaga et al 1995). Epidemiological studies were not reported any statistically significant association between CYP2E1 Rsa1 and Ins96 genotypes or CYP1A1 Val/Val genotype and gliomas (De Roos et al 2003, Trizna et al 1998).

Although, many polymorphisms have been studied their involvement in brain tumours remains unclear and controversial. Several problems, such as combined

analyses for histological subtypes, small sample size, insufficient power, mistakes in the study design or inappropriate statistical analysis might lead to wrong associations (Houston et al 2004, Bird et al 2001).

Genetics summary and suggestions for the future

In previous studies, it is suggested that genetic changes can be assumed to be a risk factor for brain tumours. Investigations suggest that mutations in p53 (Watanabe et al 2003, Harada et al 2003, Bian et al 2000, Khodarev et al 2004, Kutler et al 2003), PTENs mutations (Kraus et al 2002, Ulbricht et al 2003), mutation/homozygous deletion of Rb1 or CDKN2A, p16INK4A or amplification of CDK4 (Ichimura et al 2000, Kraus et al 2002), and genetic polymorphisms associated with basic cellular metabolic processes such as oxidation, detoxification, DNA stability and repair, and immune functioning, such as GSTP1 I105V, CYP2E1 RsaI variants and GSTT1 null genotype (de Roos et al 2003) might have an association with a raised occurrence of central nervous system (CNS) tumours. Also, 5% of brain tumours are known to have association with hereditary syndromes, such as Li-Fraumeni, tuberous sclerosis, neurofibromatosis, and Turcot syndrome (Wrensch et al 1997, Malkin et al 1990, Shepherd et al 1991, Kinzler et al 1993, Todd et al 1981).

Despite of the efforts of many investigators in the genetic area of research, the limited available findings failed to indentify major genetic factors for the aetiology of brain tumours (Houben 2006). Further studies need to be conducted, taking into account some methodological considerations and new approaches of analysis.

Methodological considerations

The first thing that is necessary to consider is the classification of brain tumours. Brain tumour studies have some problems as there is often a histologically difference between the brain tumours examined. Today, we are using the standard classification list of the World Health organisation (WHO), which is based on the knowledge we have by now of the histopathology and genetics of brain tumours (Kleihues et al 2000). The heterogeneity in morphology and malignancy grade of brain tumours, the difficulties to make an accurate diagnosis of the specific type of brain tumours, the small number of histopathological criteria to observe a classification, in addition with the fact that some brain tumours show characteristics that fit more than one type can lead to misclassifications (Kleihues et al 2000).

Another potential problem that occurs in genetic epidemiological studies is the genetic heterogeneity of brain tumours (Houben 2006). Mutations or alterations in different genes can have an involvement in the same phenotype of brain tumour. Also, it is possible these different mutations to be responsible for the development of a specific type of malignancy, but afterwards to follow a completely different genetic pathway (Kleihues et al 2000, Ohgaki et al 2005).

The difficulty to obtain substantial group of patients for the studies is another major problem that genetic epidemiology faces. The low worldwide incidence of brain tumours (3.7 per 100 000 persons-years in males and 2.6 per 100 000 persons-years in females) (CBTRUS Statistical Report 2007-2008), and the high mortality rate of the disease (5.0 per 100 000 persons- years in Great Britain) (Office of National Statistics, Mortality Statistics, England and Wales 2007, accessed February 2009) make the situation very difficult, as there is not enough time to invite participants (cases) and collect the genetic material (blood samples).

Therefore, specific large-scale multicentre projects must be designed with international collaborations in order to achieve sufficient sample of cases and be able to support the hypotheses (Wrensch et al 1997, Krishnan et al 2003, Kleinerman et al 2005, Inskip et al 2001).

Suggestions for future research

In the last years we face an evolution of genetic epidemiological methods. The complete nucleotide sequence of the human DNA is available (Venter et al 2001), an introduction to DNA microarrays for quick genotyping was made Sachidanandam et al 2001) and SNP markers and polymorphic microsatellite markers can be use achieving high rates of genotyping success (Evans et al 2004, Sawcer et al 2004). All these increase the amount of information for genetics and investigators need to focus on the data management and analysis of these outputs.

Aetiological hypotheses need to formulate regarding consistently observations of brain tumour epidemiology. Therefore, sex differences, age, geographical variations, ethnicity, deprivation category and lifestyle worth to take into account (Preston-Martin et al 1996).

In addition, a new approach of studying gene-environmental interaction should be considered with attention, as it might be the direction of the future (Brennan et al 2002). This approach should combine relevant genetic polymorphisms and environmental exposure. As we have mentioned above, in the “dietary factors” part of the chapter, there are some nutrient compounds (e.g. antioxidants) which can modulate the effects of potential carcinogens. Also, exposure to carcinogenic chemicals might have effects on susceptible genes polymorphisms, which are associated with carcinogen metabolising enzymes or DNA repair capacity. These investigations could explain the role that both genetic and environmental

exposures play in brain tumours. These studies require a large dataset, which is difficult to obtain due to the methodological considerations we have mentioned above.

A new sub-group analysis approach may be the key to unravelling the role of metabolic genes in cancer susceptibility. According to the article by Seymour Garte (2001), "when particular groups of case populations are examined separately, the importance of these genetic polymorphisms may often become quite clear". This view is supported with examples (Seymour Garte, 2001) and, even though many ethical, legal, sociological and scientific issues are raised, there is optimism that epidemiological studies of well-defined sub-groups rather than whole population may be the best path of cancer investigation.

1.3.4 Other risk factors

Radio Frequency Exposures

Many reports continue to be published suggesting that there might be health risks from exposure to radio frequency electromagnetic radiation, but the balance of evidence does not suggest RF is carcinogenic (NRPB 1993, Stewart 2000). Telecommunications devices and mobile phones suggested being a cause of brain tumours. Epidemiological studies of Telephone Company billing records in the USA (Funch et al 1996, Rothman et al 1996a, Rothman et al 1996b) did not find that using billing records was a good measure of exposure to cellular phones and no significant increased mortality was observed in mobile phone users compared to the general population. Three recently published case control studies of brain tumours and mobile phone use, including two large studies in the US, one with 782 cases and 779 controls (Inskip et al 2001) and the other one with 469 cases and 422 controls (Muscat et al 2000) and a comparatively small one from Sweden (233

cases/466 controls) (Hardell et al 1999), failed to find identify any overall increased risk for brain tumours. A further comprehensive cohort study of mobile users from Denmark found no increased risk of brain or any other cancer linked to patterns of use (Johansen et al 2001).

Occupational Chemical Exposures-Pesticides

Existing data from epidemiological studies support the hypothesis that occupational exposure to chemicals has an association with brain tumours. A review of 11 studies of the petrochemical industry (Alderson 1986) gave a combined observed/expected (O/E) of 1.16. Studies have demonstrated a range of jobs with elevated risks of brain tumours, which may involve solvent exposure (Thomas and Waxweiler 1986). A risk for vinyl chloride workers has not been substantiated (Alderson 1986, Burch et al 1987) and equivocal results are present for risks linked to the rubber industry (Thomas and Waxweiler 1986, Preston-Martin et al 1989, Burch et al 1987). Increased mortality from brain tumours has been observed in chemists and laboratory workers in different countries (Alderson 1986, Rutty et al 1991, Carpenter et al 1991) and some (Harrington and Oakes 1984, Hall et al 1991) but not all studies (Carpenter et al 1997) of pathologists. No specific common exposure has been identified.

Also, epidemiological studies indicate that occupational exposure to pesticides may play a role in the development of brain tumours. Pesticide exposure and links between brain tumours and agricultural occupations, particularly farmers, and agricultural research have emerged from several investigations (McLaughlin et al 1987, Musicco et al 1982, Ahlbom et al 1986, Morrison et al 1992, Firth et al 1996, Daly et al 1994, Jimmy T. Elfird 2003). Current information on pesticide exposure fails to provide clear evidence of a risk for brain tumours (Bohnen and Kurland 1995). According to Ana Navas –Acien et al 2002 the effect of petroleum products was independent of the intensity of ELFMF exposure whereas solvents, lead, and pesticides were only associated with glioma in workers.

Radiation

The Biological Effects of Ionizing Radiation, BEIR V report (1990) identified the brain as a radiosensitive organ at risk of malignancy following high doses of ionising radiation in utero. Exposure to dental x-rays appears to increase the risk of developing a brain tumour in some studies (Neuberger et al 1991), but not in others (Schlehofer et al 1992, Ryan et al 1992) and therapeutic CNS radiation may increase the risk of developing a primary cerebral tumour (Hodges et al 1992). A 15 per cent excess mortality from brain tumours was observed in a large cohort study of American nuclear workers (1.6 million person years of observation) suggesting a risk for exposure to accumulated low doses (Alexander 1991).

Head Trauma

Individual studies have demonstrated a relationship between serious head injury and meningiomas (not gliomas) (Preston-Martin et al 1989) and intracranial vascular tumours (Inskip et al 1998). A Catharina Nygren et al 2001 study found no association between traumatic brain injury and brain tumours. Serious trauma to the head should be accounted for in future investigations.

Viruses

Animal models have provided limited support to the hypothesis that viruses may be involved in the aetiology of brain tumours (Schoenberg 1982). In general, epidemiological studies have been inadequate to clarify this, although a recent study in the US showed no evidence of a link between polio vaccine contaminated with SV 40 and brain tumours (Strickler et al 1998). Two laboratory investigations have found integrated SV 40 viral sequences in tumour tissue of ependymomas and choroids plexus papillomas (Bergsagel et al 1992, Lednicky et al 1995). This remains an issue of interest.

1.4. AIMS

The aim of this study is to investigate the link between cumulative electromagnetic field (EMF) exposure, which reflected lifetime exposure, rather than electromagnetic field (EMF) exposure from any specific job and glioma, meningioma and acoustic neuroma.

Chapter 2

Design and Methods

2. Design and Methods

This chapter describes the background of the UK Adults Brain Tumour Study (UKABTS). Based on the protocol and previous studies of the UK Adults Brain Tumour Study (UKABTS) (Hepworth et al 2006a, Hepworth et al 2006b), we report the procedure for the selection of cases and controls. This chapter is followed by information for the occupational and diet data collection. Finally, methods for calculating the exposure to electromagnetic fields are explained, as well as the analysis plan we followed to investigate the association of electromagnetic fields (EMF) with brain tumours.

2.1 Ethics Approval

The study has been approved by the Multi-Centre Research Ethics Committee (MREC) for Scotland (reference MREC/99/0/77). All relevant Local Medical Research Ethics Committees and hospital trust ethics committees in the study areas have been approached and given their approval.

2.2 Study background and design

In 2001, the UK Adult Brain Tumour Study (UKABTS) began to investigate the role of a number of environmental agents in the onset of brain cancer. The study is the collaboration between three institutes including the Department of Epidemiology and Public Health of University of Nottingham, the Centre for Occupational and Environmental Health of University of Manchester and the Unit of Epidemiology and Health Services Research of Leeds University. The UKABTS is part of an international case-control study of adult brain tumours (the INTERPHONE study), co-ordinated at the International Agency for Research on Cancer (IARC). The

INTERPHONE was set up to investigate the association between mobile phone use and incidence of brain cancers (Cardis and Kilkenny, 1999).

The UKABTS is a case-control study. The study was conducted in four centres: central Scotland, Trent, West Midlands and West Yorkshire (Hepworth et al., 2006a; Hepworth et al., 2006b). All cases and controls were interviewed by trained interviewers, using a computer assisted personal interview (CAPI) system (Hepworth et al., 2006b). In addition to demographics, health information and information on the use of mobile phones, data were also collected on occupational sources of electromagnetic fields and diet. A full occupational history of all jobs held longer than 12 months from leaving school to the present day was obtained by self administered questionnaire, sent to respondents prior to the interview. Data for EMF exposure required Job title, industry, date of starting and finishing each job. After a face to face interview each participant was left a food frequency questionnaire (FFQ) on dietary intake to complete and return by post to the study centre. Participants were asked to recall their diet in the past two years. Blood samples are taken from more than 90% of cases and controls, and serum and DNA stored to investigate genetic predisposition and viral status.

Eligible cases were aged 18-69 years and resident in the study areas, first diagnosed between 1st December 2000 and 30th June 2003, with glioma (ICDO-3 topography:C71, morphology: 9380-9411,9420-9451,9480,9505), meningioma (topography: C70.0, morphology: 9530-9539) or acoustic neuroma (topography: C72.4, morphology: 9560/0) (World Health organization, 2000).

2.3.1 Selection of cases

Incident cases from a defined geographical area were defined according to the following criteria:

1) Diagnosis:

a) a histologically confirmed primary intracranial tumour

b) tumours diagnosed by scans and radio imaging

c) localisation of tumours

2) Age: Between 18 and 69 years old at the time of diagnosis, to allow a reasonable period of occupational exposure.

3) Geographical area: Living in one of the 4 study areas (Central Scotland, West Yorkshire, Trent, West Midlands).

Multiple sources were used for case finding through active mechanisms and seek collaboration with treating centres. Case ascertainment was proactive and rapid, aiming to have notifications within 3 weeks of diagnosis. A feasibility study had established the mechanism of collaboration and the enthusiastic support of clinicians. Neurosurgeons, neurologists, neuro-radiologists, neuro-oncologists, neuro-pathologists and Cancer Registries were all to provide notifications and the required information. Many centres had multidisciplinary teams involved in treatment that facilitated case ascertainment and local arrangements had been made to take account of the wishes of the clinical collaborators and their staff. Systematic crosschecks with the cancer registries optimised ascertainment and ensured that the proportion of interviewed cases in the population could be calculated.

Eligible cases were approached through their treating consultants. Surrogate interviews were undertaken as an alternative for those with conditions which made interview impossible or for those who had died.

2.3.2 Selection of controls

Controls were population-based and the eligibility criteria for the controls were set as follows:

Control ascertainment - procedures for selection varied slightly by region but all achieved the following:

- Random selection of a set of eligible controls from an entire GP practice list either where the case was registered or a practice nearby.
- Each control was matched with one case of the same age or up to one year older and of the same sex.

Approach to controls was also done through their GP and by letter and their participation in the study was entirely voluntary.

2.3.3 Occupational Data

The occupational data were obtained by a self administered questionnaire that was sent to respondents prior to the interview. They were asked to give a full occupational history of all jobs held longer than 12 months from leaving school to the present day. Participants were asked to complete an occupational calendar where job title, industry, date of starting and finishing each job were required. All occupational calendars were collected from the trained interviewers at the end of each face to face interview.

Coding of Occupational Histories

All occupations in the occupational calendar were coded by the study interviewers according to the Standard Industrial Classification (SIC) (The Office for National Statistics, 1992) and the Standard Occupational Classification (SOC) (The Office for National Statistics, 2000). The completion of SIC and SOC codes was checked.

2.3.3.1 Scoring occupational exposure to electromagnetic fields

In this study, using the secondary occupational data, my role was to score the exposure to electromagnetic fields and then to conduct a statistical analysis to see whether occupational exposure to EMF is a potential risk factor for brain tumours. First of all, an appropriate geometric mean (GM) of electromagnetic field exposure had to be given for each Standard Industrial Classification (SIC) and each Standard Occupational Classification (SOC) code. My involvement was to link these SIC and SOC codes with the appropriate geometric mean of the exposure.

Each Standard Industrial Classification (SIC) and each Standard Occupational Classification (SOC) code was allocated electromagnetic fields (EMF) Geometric mean from a previous analysis that searched for determinants of occupational exposure to extremely low frequency electromagnetic fields in the general population in the UK (Van Tongeren et al., 2007). There were 1240 of 9992 job subjects whose SOC codes could not be matched with the existing list of electromagnetic fields (EMF) geometric means. These SOC codes were linked with the UKSoc2000 list (SOC code list 2000) and the US80 list (SOC code list) in order to classify them in an occupational category that a geometric mean of electromagnetic field exposure exists. Since the two lists were to some extent different, the ISCO88 (a list matching the soc codes for USA and UK), was applied to aid the coding procedure. Ultimately, some SOC codes were still unable to be matched, so the geometric mean of exposure for these codes reported as missing. This procedure helped to reduce the number of subjects with missing EMF data and optimized the use of available data. This procedure cannot be applied with SIC codes as there is no specific list linking the UK SIC codes and the US SIC codes.

According to the Standard Industrial Classification (SIC), the minor group with the highest geometric mean of exposure to electromagnetic fields is the “electricity

generation and supply" (SIC: 40, geometric mean: 1.58), followed by the minor group of "publishing, printing, reproduction" (SIC: 22, geometric mean: 0.27). The minor groups of "hotels and restaurants" (SIC: 55) and "manufacture of basic and fabricated metals" (SIC: 27-28) have also a high geometric means, GM: 0.20 and GM: 0.18 respectively.

For the Standard Occupational Classification (SOC) the minor group of "managers in hospitality and service industry" (SOC: 122, 123) has the highest geometric mean of exposure (GM: 0.19), followed by the minor group of "other manufacture" (SOC: 541, 524, 549, 8111, 8116) with geometric mean 0.19. The groups of "metal and vehicle workers" (SOC: 521-523, 8117, 812, 813) and "administrative jobs" (SOC: 1, 42) have geometric mean of exposure 0.13. The group of "electrical trades" (SOC: 524) has also a high geometric mean of exposure (GM: 0.12). Also, "construction" (SOC: 531, 814) and "packers, warehouse" (SOC: 13, 914) groups have geometric mean of exposure to electromagnetic fields 0.10.

The Standard Occupational Classification (SOC) list focuses on the job title and the description of the work each person is doing in order to classify the occupation groups. On the other hand, Standard Industrial Classification (SIC) codes indicate the company's type of business. Therefore, each group might have different occupations and this can be an explanation for possible differences between geometric means of exposure to electromagnetic fields of similar groups by SIC and SOC codes. For example the "electricity generation and supply" group of SIC list has geometric mean 1.58, but the group of "electric trades" of SOC list has geometric mean 0.12. Despite this, the geometric means of exposure of similar SIC and SOC groups do not have much difference, especially for groups with low exposure to electromagnetic fields.

The cumulative exposure to EMF for each participant, was calculated using the mathematical formula

$$\sum_{i=1}^{n} \text{geometric mean for each jobtitle} \times \text{total months} \div 12 \times 286 \text{ days}$$

where n= the number of jobs each participant has held.
The total working days for British people is 286 days from 365 (365 [total days in 1 year] – 56 [Saturday and Sunday for all 12 months] -8 [official bank holidays] -15 [the entitlement for 3 weeks holiday including 5 working days per week with Saturdays and Sundays not included as they were already excluded from the total of 12 months]). No off sick days were accounted for. The geometric mean for electromagnetic field exposure for each job was based on the SIC and SOC codes. With this formula, each participant has a cumulative exposure to EMF depending on the jobs he/she had had up to the data collection date.

2.3.3.2 Statistical analysis

An epidemiological (case-control) analysis was conducted to establish occupational exposure to electromagnetic fields effect on brain tumours. This analysis carried out in SPSS and provided OR estimates 95% confidence intervals (CI) and significance levels.

Descriptive statistical models were used to check for frequencies and to summarise the baseline characteristics of the study population. Histograms did not support a normal distribution of electromagnetic field (EMF) data and a non parametric test was employed to check the differences in rankings of electromagnetic fields exposure.

To assess estimated risks, the total EMF for both SIC and SOC codes for all subjects was categorised into quartiles, based on control group quartile distribution. Collectively, an unconditional logistic regression adjusted for age (5 year age groups), sex, region (n=4), and deprivation category based on Townsend score (n=5) (Townsend, 1987) was carried out. Analyses were also carried out to

assess the risk for each type of brain tumour including glioma, meningioma and acoustic neuroma.

2.4 Power of the study – all outcomes included

In case-control studies, it is not possible to directly estimate disease incidence in those exposed and those unexposed, since people are selected on the basis of having or not having the condition of interest, not on the basis of their exposure status. It is, however, possible to calculate the odds of exposure in the cases and in the controls. The power of a case-control study is defined as the probability that a significant difference will be found between the case and control groups, given that a true difference exists.

As we have mentioned in the previous section, limited data exist regarding association between occupational exposure to electromagnetic fields and brain tumours. All previous studies were looking at specific rather than lifetime exposure to electromagnetic fields; therefore there is no evidence of how big is the effect of lifetime occupational exposure to electromagnetic fields to the risk of having brain tumour. Considering that odds ratios are higher when we study the association between exposure to electromagnetic fields for specific occupations and the risk of brain tumour, instead of lifetime exposure to electromagnetic fields, we select an odd ratio of 1.5 for the effect estimate we intended to detect in our study.

The total number of 2067 subjects (970 cases and 1097 controls) that included in the statistical analysis allows us to have 95% power of detecting a relative risk of 1.5, at 5% level of significance. Therefore, for the entire group of all brain tumours, the study has sufficient power. There are 588 gliomas included in the analysis comprising approximately the 60% of all cases. Even for this restricted

group we can estimate sufficient power of 95% of detecting a relative risk of 1.5, at 5% level of significance. Smaller sub-groups of tumours (247 meningiomas and 135 acoustic neuromas) will have reduced power (approximately 86% for meningiomas and approximately 77% for acoustic neuromas) to detect risks as low as 1.5, at 5% level of significance.

Chapter 3

Results

3. Results of electromagnetic fields exposure and the risk of brain tumours

This chapter presents the results from the statistical analysis that was conducted to find association between electromagnetic fields exposure and brain tumours. Demographic information as well as participation and refusal numbers is demonstrated. Mean and median values for cumulative electromagnetic fields exposure have been compared between cases and controls. Finally, the distribution of subjects by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes based on quartiles distribution and the estimated risks for the occupational and industrial exposure to electromagnetic fields (EMF) is presented.

Participation and demographic information for overall population

In the UK Adults Brain Tumour Study (UKABTS) 1408 cases and 2491 controls were selected. From the 1408 cases the 946 were gliomas, the 310 meningiomas and the 152 acoustic neuromas. Finally, the participants in the study were 978 cases and 1100 controls. The response rate was approximately 70% among cases and 44% among controls. The main reasons for not taking part for controls was non-response (26%) or refusal (22%), whilst for the cases the main reasons for non-response were death/too ill (19%) and refusal (11%). The following table (Table 3.1) summarises the information on participation and refusal in the UK Adults Brain Tumour Study.

TABLE 3.1 Participation and refusal info in the UK Adults Brain Tumour Study (UKABTS)

	Cases n(%)	Glioma n (%)	Meningioma n (%)	Acoustic Neuroma n (%)	Control n (%)
All eligible participants	978(70)	593 (63)	250 (81)	135(89)	1100(44)
Participants with exposure information	499(35)	247 (26)	167 (54)	85 (56)	1033(41)
Non-participants					
Consultant/ GP	29(2)	26 (3)	3 (1)	0 (0)	179(7)
Deceased/ too ill	197(14)	183(19)	14 (5)	0 (0)	4(<1)
Non-response	32(2)	22 (2)	8 (3)	2 (1)	658(26)
Refusal	149(11)	103(11)	32(10)	14 (9)	538(22)
Other	17(1)	13 (2)	3 (1)	1 (1)	9 (<1)
No occupational calendar	6(<1)	6 (<1)	0 (0)	0 (0)	3 (<1)
Total	1408(100)	946(100)	310(100)	152(100)	2491(100)

In this study a total number of 2067 subjects (970 cases and 1097 controls) were included in the statistical analysis (gliomas n=588; meningiomas n=247; acoustic neuromas n=135; controls=1097). That shows that there was a loss of only 8 cases and 3 controls of the participants in the main UK Adults Brain Tumour Study (UKABTS). This is a very small number of subjects without occupational calendar; represent less than 1% of all participants. Due to this fact our results have no lost of power.

Table 3.2 provides demographic information on the participants. Approximately, 62% of gliomas cases were male, whilst for the meningiomas and acoustic neuromas the majority was female (74.1% and 57.0% respectively). There was

approximately equal proportion of males and females (50%) among all cases, as well as among the controls. Independent age distribution for all cases and controls was not diverged, as for each 5-years age group approximately equal proportion of cases and controls were seen. Most of the cases and controls were ranged between the ages of 50 to 64. Approximately the same age distribution was seen for the subgroup of gliomas compared to controls. At the age range of 45 to 64 a higher proportion was seen for meningiomas (age 45-49: 13.8%, age 50-54: 19%, age 55-59: 17.4%, age 60-64: 17.8%, age 65-69: 6.9%) compared to controls (age 45-49: 12.2%, age 50-54: 17.5%, age 55-59: 16.8%, age 60-64: 15.5%, age 65-69: 5.7%). For acoustic neuromas a higher proportion compared to controls was seen at the age range of 35 to 49 (age 35-39: acoustic neuromas 13.3%-controls 9.1%, age 40-44: acoustic neuromas 14.8%-controls 10.5%, age 45-49: acoustic neuromas 13.3%-controls 12.2%). A higher proportion of both cases and controls were seen in the most affluent Townsend score compared to the other points of Townsend score (all cases 26.9 %; gliomas 28.4 %; meningiomas 24.7 %; acoustic neuromas 24.4% and controls 29.8%). A higher proportion of controls were classified in the most affluent Townsend score compared to cases, especially when compared to meningiomas and acoustic neuromas cases. A higher proportion of both cases and controls were seen for region of Trent (all cases 34.4%; gliomas 33.7%; meningiomas 38.5%; acoustic neuromas 30.4% and controls 33.9%). The region of West Midlands has the less proportion of all cases (17.5%), gliomas (18.9%), meningiomas (10.5%) and controls (18.6%), and only for acoustic neuromas the less proportion were seen for the region of West Yorkshire (16.3%).

Table 3.2. Demographic information for all study participants

	All cases (n=970)	Glioma (n=588)	Meningioma (n=247)	Acoustic Neuroma (n=135)	Control (n=1097)
	All n (%)	All n (%)	All n (%)	All n (%)	All n (%)
Sex					
Male	487 (50.2)	365 (62.1)	64 (25.9)	58 (43.0)	543 (49.5)
Female	483 (49.8)	223 (37.9)	183 (74.1)	77 (57.0)	554 (50.5)
Age (5 years group)					
18-29	59 (6.1)	43 (7.3)	7 (2.8)	9 (6.7)	70 (6.4)
30-34	61 (6.3)	42 (7.1)	10 (4.0)	9 (6.7)	70 (6.4)
35-39	88 (9.1)	53 (9.0)	17 (6.9)	18 (13.3)	100 (9.1)
40-44	103 (10.6)	55 (9.4)	28 (11.3)	20 (14.8)	115 (10.5)
45-49	117 (12.1)	65 (11.1)	34 (13.8)	18 (13.3)	134 (12.2)
50-54	171 (17.6)	104 (17.7)	47 (19.0)	20 (14.8)	192 (17.5)
55-59	167 (17.2)	105 (17.9)	43 (17.4)	19 (14.1)	184 (16.8)
60-64	149 (15.4)	85 (14.5)	44 (17.8)	20 (14.8)	170 (15.5)
65-69	55 (5.7)	36 (6.1)	17 (6.9)	2 (1.5)	62 (5.7)
Region					
1 Scotland	255 (26.3)	150 (25.5)	66 (26.7)	39 (28.9)	280 (25.5)
2 West Yorkshire	211 (21.8)	129 (21.9)	60 (24.3)	22 (16.3)	241 (22.0)
3 West Midlands	170 (17.5)	111 (18.9)	26 (10.5)	33 (24.4)	204 (18.6)
4 Trent	334 (34.4)	198 (33.7)	95 (38.5)	41 (30.4)	372 (33.9)
Deprivation score					
1 (most affluent)	261 (26.9)	167 (28,4)	61 (24.7)	33 (24.4)	327 (29.8)
2	227 (23.4)	136 (23.1)	62 (25.1)	29 (21.5)	247 (22.5)
3	166 (17.1)	99 (16.8)	40 (16.2)	27 (20.0)	199 (18.1)
4	184 (19.0)	108 (18.4)	45 (18.2)	31 (23.0)	183 (16.7)
5 (least affluent)	132 (13.6)	78 (13.3)	39 (15.8)	15 (11.1)	141 (12.9)

Cumulative electromagnetic field exposure

Figures 3.1 are histograms of the distribution of total electromagnetic field exposure by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) between cases-controls and diagnosis groups (gliomas, meningiomas, acoustic neuromas). The plots showed data are not normally distributed and therefore to compare means between cases and controls, non-parametric test was used. In figure 3.1.1 is the distribution of total electromagnetic field exposure calculated by SOC codes among all participants and in figure 3.1.2 the distribution of total electromagnetic field exposure calculated by SIC codes among all participants. The distributions of total electromagnetic field exposure by SOC codes among cases and controls demonstrated in figure 3.1.3 and among cases subtypes (gliomas, meningiomas, acoustic neuromas) and controls in figure 3.1.4. Figure 3.1.5 shows the distributions of total electromagnetic field exposure by SIC codes among cases and controls and figure 3.1.6 among cases subtypes (gliomas, meningiomas, acoustic neuromas) and controls.

Figure 3.1.1 Distribution of total electromagnetic fields exposure by SOC codes among all participants

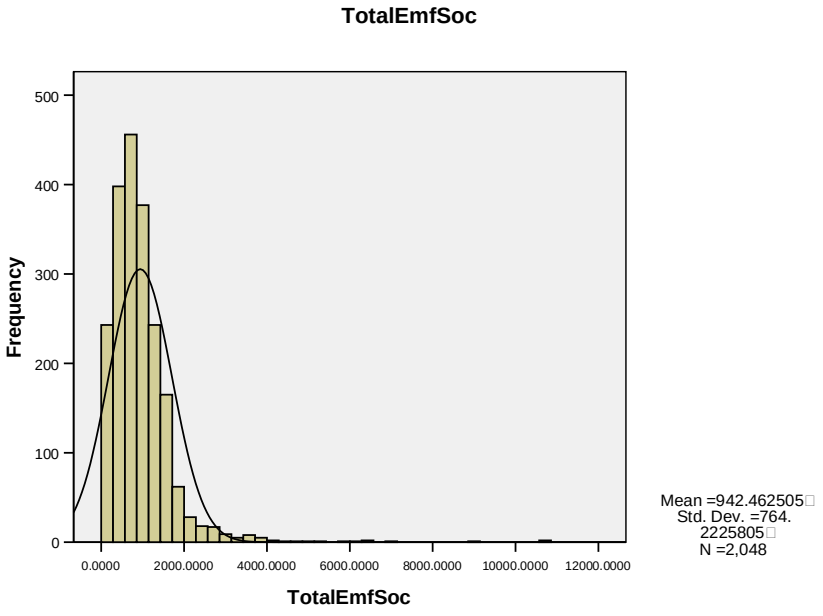
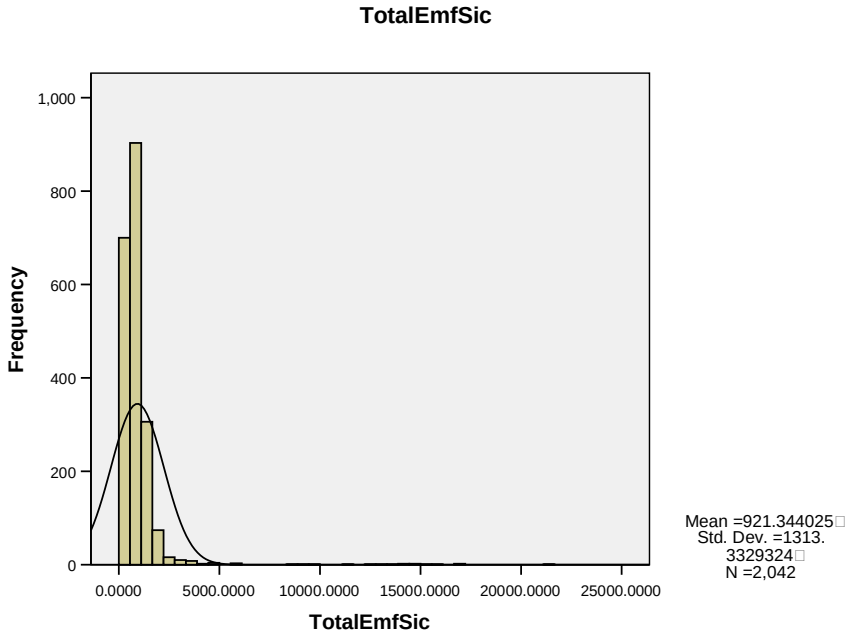
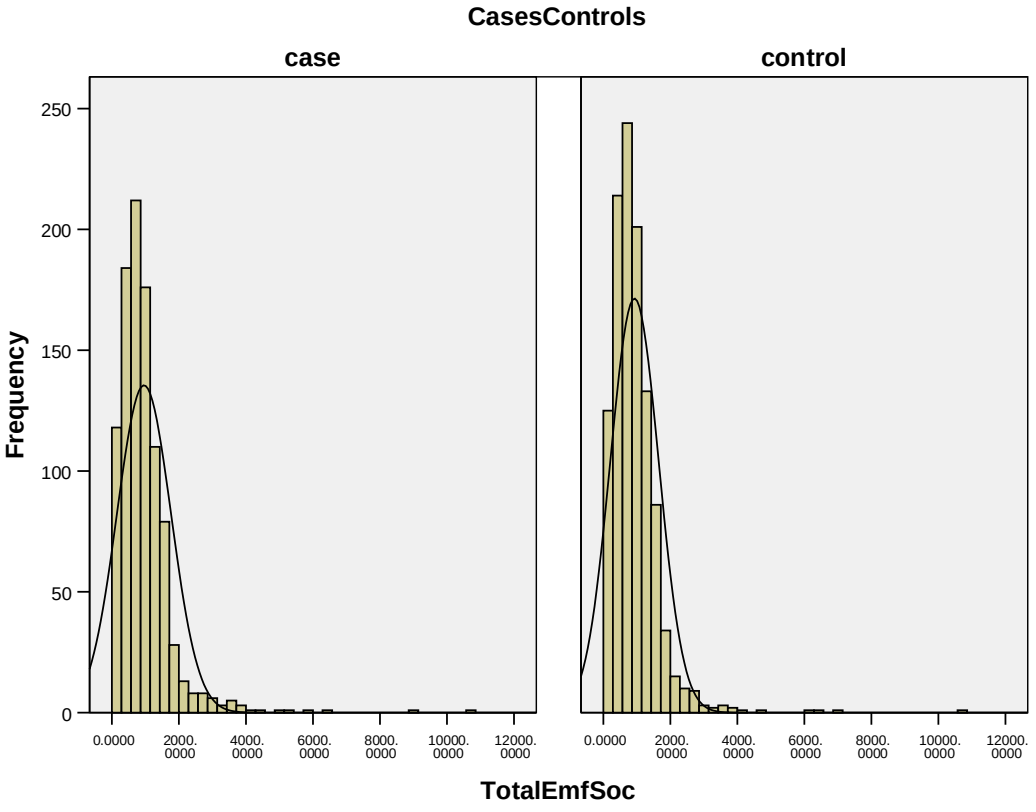


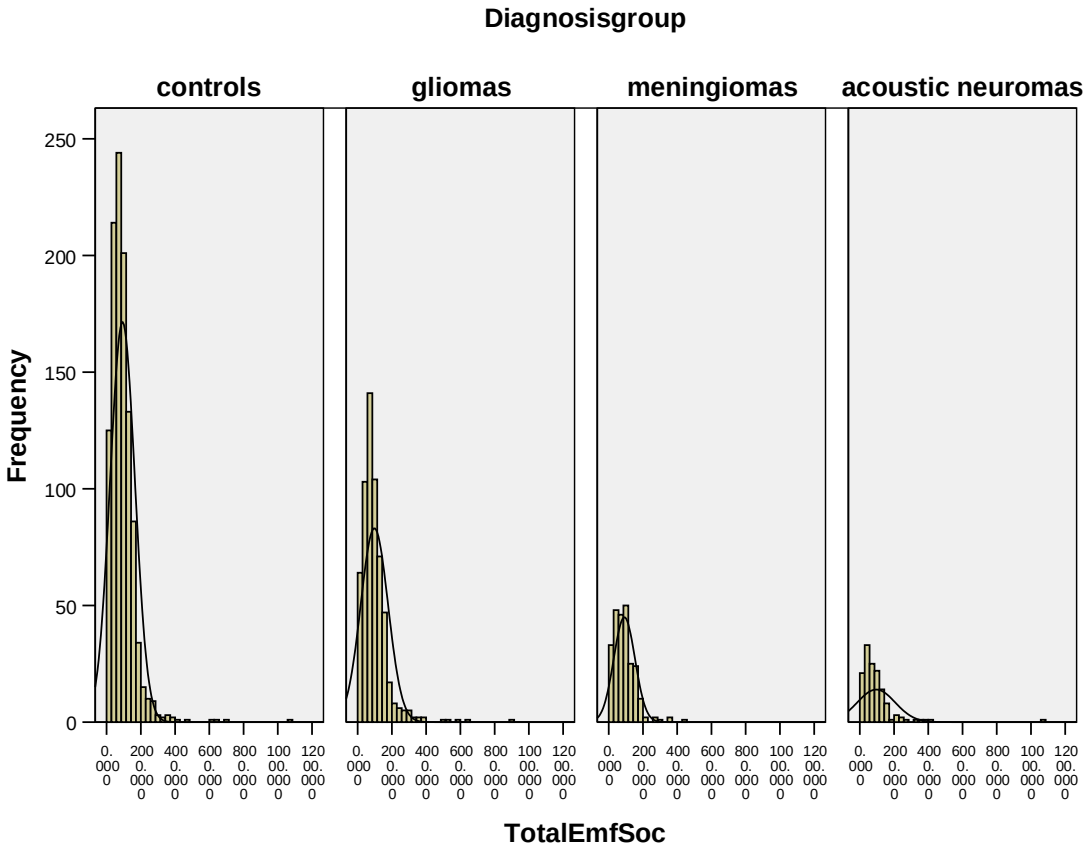
Figure 3.1.2 Distribution of total electromagnetic field (EMF) exposure by SIC codes among all participants



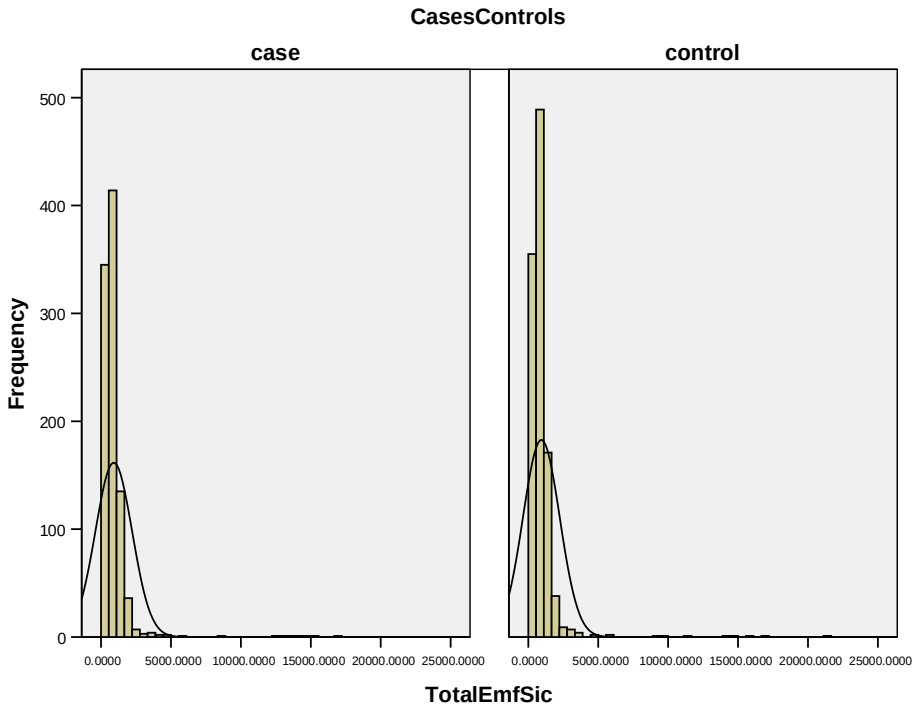
Figures 3.1.3 Distribution of total electromagnetic field exposure by SOC codes among cases and controls



Figures 3.1.4 Distribution of total electromagnetic field exposure by SOC codes among cases subtypes (gliomas, meningiomas, acoustic neuromas) and controls



Figures 3.1.5 Distribution of total electromagnetic field exposure by SIC codes among cases and controls



Figures 3.1.6 Distribution of total electromagnetic field exposure by SIC codes among cases subtypes (gliomas, meningiomas, acoustic neuromas) and controls

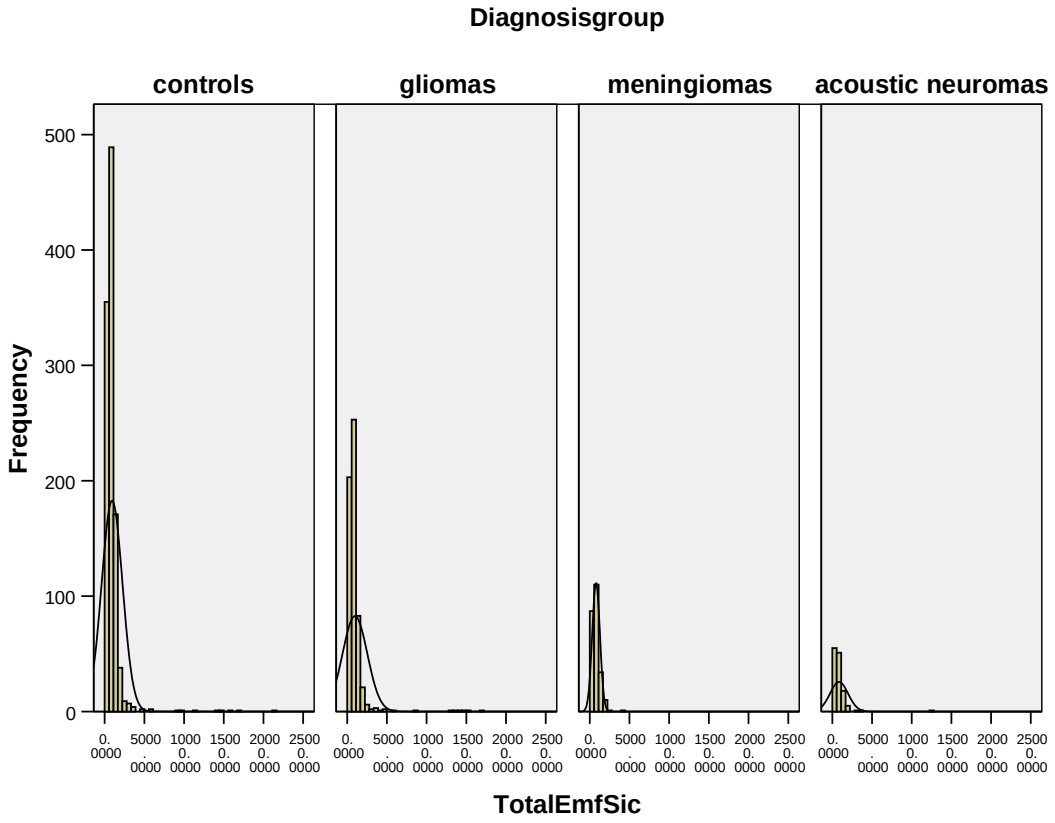


Table 3.3 shows the statistic for cumulative electromagnetic field exposure estimates based on the two methods, industry or occupational classification. In our analysis for cumulative exposure to electromagnetic fields by occupation (by SOC code) and the risk of developing brain tumours, the SOC code 9129 (12 subjects of the total 9992 job subjects) was excluded as after matching this specific code with the US80 code, the geometric mean (GM) for this code was extremely high (593,403), and including the values in the dataset obviously would create a large standard deviation around the means. The percentage of missing data for SIC codes is 6.05% and for SOC codes is 3.39%. Comparing the medians of cumulative electromagnetic fields exposure by industry, all cases, gliomas and acoustic neuromas had a smaller median than the one of controls. The median of acoustic neuromas has the higher difference compared to the median of controls (acoustic

neuromas: median 613.99 –controls: median 749.320). The median of exposure for meningiomas is approximately the same with the one of controls.

For cumulative EMF exposure by occupation, glioma cases had higher median value than controls (Gliomas: median 827.600 – Controls: median 804.256). Meningiomas had a higher median than controls (Meningiomas: median 811.573 – Controls: median 804.256). The median of acoustic neuromas was smaller compared to the one of controls (Acoustic neuromas: median 709.280 – Controls: median 804.256). There was no difference between the Standard Occupational Classification (SOC) and the Standard Industrial Classification (SIC) electromagnetic fields (EMF) exposure means for the case and control groups (Mann-Whitney U test, p-value >0.05).

Table 3.3. Statistics of cumulative electromagnetic field (EMF) exposures by SIC and SOC codes

	All cases (n=970)	Glioma (n=588)	Meningioma (n=247)	Acoustic Neuroma (n=135)	Control (n=1097)
EMFSIC					
Mean	908.061	971.532	791.535	842.726	933.060
Median	718.241	725.332	750.035	613.399	749.320
Min	4.004	4.004	40.040	4.505	22.880
Max	16898.830	16898.830	4251.938	12227.740	21238.360
SD	1311.964	1559.521	479.929	1140.890	1315.033
Missing	13	6	4	3	12
EMFSOC					
Mean	957.758	976.321	912.937	958.745	928.940
Median	809.261	827.660	811.573	709.280	804.256
Min	0.000	23.786	0.000	8.366	0.000
Max	10578.660	8947.663	4370.044	10578.660	10743.030
SD	808.510	798.665	619.077	1103.315	722.919
Missing	9	6	3	0	10

Table 3.4 shows the frequency numbers for the diagnosis groups (controls, all cases, gliomas, meningiomas, acoustic neuromas) by SIC and SOC based on quartiles distribution. Cut-off points for EMF exposure quartiles were based on the frequency of EMF exposure in the controls subjects. The lowest quartile (Q1) was the reference category. For total EMF exposure by industry and by occupation the distribution in the first quartile is higher than in the other ones for all cases and for gliomas, meningiomas and acoustic neuromas (Total EMF SIC - Q1: all cases 28.8%, gliomas 28,2%, meningiomas 26,7%, acoustic neuromas 35,6%, Total EMF SOC – Q1: all cases 26,3%, gliomas 23,5%, meningiomas 27%, acoustic neuromas 37%). Especially for acoustic neuromas the distribution in the first quartile for total EMF exposure by industry and by occupation is very high than in the others quartiles. This abnormality to the distribution might influence our results.

Table 3.4. Frequency numbers for diagnosis groups by sic and soc codes in quartiles

	All cases	Glioma	Meningioma	Acoustic Neuroma	Control
TEMFSIC					
Q1	276 (28,8)	164 (28,2)	65 (26,7)	47 (35,6)	271 (25,0)
Q2	234 (24,5)	147 (25,3)	56 (23,0)	31 (23,5)	271 (25,0)
Q3	227 (23,7)	133 (22,9)	68 (28,0)	26 (19,7)	272 (25,1)
Q4	220 (23,0)	138 (23,7)	54 (22,2)	28 (21,2)	271 (25,0)
Total	957 (100)	582 (100)	243 (100)	132 (100)	1085 (100)
Missing: 25 (1,2%)	13	6	4	3	12
TEMFSOC (9129 excluded)					
Q1	253 (26,3)	137 (23,5)	66 (27,0)	50 (37,0)	271 (24,9)
Q2	224 (23,3)	141 (24,2)	55 (22,5)	28 (20,7)	272 (25,0)
Q3	241 (25,1)	153 (26,3)	63 (25,8)	25 (18,5)	272 (25,0)
Q4	243 (25,3)	151 (25,9)	60 (24,6)	32 (23,7)	272 (25,0)
Total	961 (100)	582 (100)	244 (100)	135 (100)	1087 (100)
Missing: 19 (0,9%)	9	6	3	0	10

Tables 3.5 (3.5.1-3.5.8) show the distribution of subjects by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes based on quartiles distribution and the estimated risks for the occupational and industrial exposure to electromagnetic fields (EMF). The lowest quartile (Q1) was used as the reference category. For total electromagnetic field (EMF) exposure by industry and by occupation, the distribution of cases in the first quartile is the highest regardless of tumour type.

Table 3.5.1 showed the results for all brain tumour cases and the exposure to electromagnetic fields by industry (by SIC). The unadjusted crude odd ratios even though indicate a weak inverse association between electromagnetic field exposure and brain tumours were not statistically significant (p-value> 0.05). When the electromagnetic field exposure increases, the risk of developing brain tumour slightly decreases (Q2: OR 0.85, 95% CI (0.67-1.08), p-value 0.182 – Q3: OR 0.82, 95% CI 0.64-1.05, p-value 0.109 and Q4: OR 0.79, 95% CI 0.62-1.01, p-value 0.069). A modest statistically significant decreased risk was observed in the 3rd and 4th quartile for adjusted model results for electromagnetic fields exposure by industry (by SIC) (Q3: OR 0.73, 95% CI 0.55-0.97 and Q4: OR 0.70, 95% CI 0.52-0.94). There was evidence of risk decreasing across all quartiles (p for trend 0.019).

3.5.1 Total EMF exposure classified by SIC codes and all brain tumours risk

EMF exposure	Control (n= 1085)	Case (n= 957)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	276	1.00		1.00	
Q2	271	234	0.85 (0.67-1.08)	0.182	0.80 (0.62-1.05)	0.103
Q3	272	227	0.82 (0.64-1.05)	0.109	0.73 (0.55-0.97)	0.032
Q4	271	220	0.79 (0.62-1.01)	0.069	0.70 (0.52-0.94)	0.017
p-trend						0.019

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Table 3.5.2 showed the results for gliomas and their association with exposure to electromagnetic fields by industry (by SIC). For the unadjusted model even though there was a weak inverse association between exposure and the risk of developing glioma the odd ratios were not statistically significant (Q2: OR 0.89, 95% CI 0.68-1.18, p-value 0.442 –Q3: OR 0.81, 95% CI 0.61-1.07, p-value 0.141 and Q4: OR 0.84, 95% CI 0.64-1.12, p-value 0.231). The adjusted odd ratios showed that participants with exposure to electromagnetic fields in the 3rd quartile are 28% less likely to develop glioma and for those in the 4th quartile 29% less likely (Q3: OR 0.72, 95% CI 0.51-1.01 and Q4: OR 0.71, 95% CI 0.45-1.00). A clear trend of risk reduction across quartiles was obtained (p for trend 0.03).

3.5.2 Total EMF exposure classified by SIC codes and risk of developing gliomas

EMF exposure	Control (n=1085)	Case (n=582)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	164	1.00		1.00	
Q2	271	147	0.89 (0.68-1.18)	0.442	0.87 (0.64-1.19)	0.402
Q3	272	133	0.81 (0.61-1.07)	0.141	0.72 (0.51-1.01)	0.059
Q4	271	138	0.84 (0.64-1.12)	0.231	0.71 (0.45-1.00)	0.049
p-trend						0.034

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Table 3.5.3 shows the results obtained for electromagnetic field exposure by industry and the risk to develop meningioma. No association was found between exposure to electromagnetic fields (by SIC) and meningiomas. The unadjusted and adjusted odd ratios were not statistically significant, as well as the p for trend (p-trend=0.44>0.05). For the unadjusted model the results for the 2nd quartile were Q2: OR 0.86, 95% CI 0.58-1.28, p-value 0.460, for the 3rd quartile Q3: OR 1.04, 95% CI 0.71-1.52, p-value 0.830 and for the 4th quartile Q4: OR 0.83, 95% CI

0.56-1.24, p-value 0.362. For the adjusted model even though the odd ratios were indicating that exposure to electromagnetic fields decrease the risk of developing meningiomas, the results were not statistically significant (Q2: OR 0.74, 95% CI 0.48-1.13, p-value 0.157 – Q3: OR 0.87, 95% CI 0.56-1.36, p-value 0.550 and Q4: OR 0.77, 95% CI 0.48-1.24, p-value 0.283).

3.5.3 Total EMF exposure classified by SIC codes and risk of developing meningiomas

EMF exposure	Control (n=1085)	Case (n=243)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	65	1.00		1.00	
Q2	271	56	0.86 (0.58-1.28)	0.460	0.74 (0.48-1.13)	0.157
Q3	272	68	1.04 (0.71-1.52)	0.830	0.87 (0.56-1.36)	0.550
Q4	271	54	0.83 (0.56-1.24)	0.362	0.77 (0.48-1.24)	0.283
p-trend						0.44

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Table 3.5.4 demonstrates the results for electromagnetic field exposure by industry (by SIC) and the risk factor to develop acoustic neuromas. For acoustic neuromas, the unadjusted model showed the inverse associations in the 3rd and 4th quartile (Q3: OR 0.55, 95% CI 0.33-0.92 and Q4: OR 0.59, 95% CI 0.36-0.98). Crude odd ratios showed that exposure to electromagnetic fields seem to be protective, as subjects who are in the quartiles with the high exposure are 45% (for 3rd quartile) and 41% (for 4th quartile) less likely to develop acoustic neuromas. The effects disappeared when adjusted for confounding factors, as the adjusted odd ratios were not statistically significant (Q3: OR 0.59, 95% CI 0.33-1.06, p-value 0.083 and Q4: OR 0.67, 95% CI 0.37-1.23, p-value 0.198). Collectively, there was no evidence of risk decreasing across quartiles (p for trend 0.185).

3.5.4 Total EMF exposure classified by SIC codes and risk of developing acoustic neuromas

EMF exposure	Control (n=1085)	Case (n=132)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	47	1.00		1.00	
Q2	271	31	0.66 (0.41-1.07)	0.092	0.66 (0.39-1.11)	0.116
Q3	272	26	0.55 (0.33-0.92)	0.021	0.59 (0.33-1.06)	0.083
Q4	271	28	0.59 (0.36-0.98)	0.041	0.67 (0.37-1.23)	0.198
p-trend						0.185

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Table 3.5.5 indicates the results for all brain tumour cases and the exposure to electromagnetic fields by occupation (by SOC). The unadjusted odd ratios showed no association (Q2: OR 0.88, 95% CI 0.69-1.13, p-value 0.318 – Q3: OR 0.95, 95% CI 0.74-1.21, p-value 0.674 and Q4: 0.96, 95% CI 0.75-1.22, p-value 0.723). Also, for adjusted model no association was observed (Q2: OR 0.86, 95% CI 0.66-1.12, p-value 0.257 – Q3: OR 0.91, 95% CI 0.69-1.21, p-value 0.510 and Q4: OR 0.91, 95% CI 0.68-1.22, p-value 0.531). Overall, no statistically significant associations were found between exposure to electromagnetic fields by Standard Occupational classification (SOC) coding and brain tumours. Also there was no evidence of risk across quartiles (p-trend 0.70).

3.5.5 Total EMF exposure classified by SOC codes and brain tumours risk

EMF exposure	Control (n=1087)	Case (n=961)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	253	1.00		1.00	
Q2	272	224	0.88 (0.69-1.13)	0.318	0.86 (0.66-1.12)	0.257
Q3	272	241	0.95 (0.74-1.21)	0.674	0.91 (0.69-1.21)	0.510
Q4	272	243	0.96 (0.75-1.22)	0.723	0.91 (0.68-1.22)	0.531
p-trend						0.70

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

For the subgroup of gliomas and the association with exposure to electromagnetic fields by occupation (by SOC) no statistically significant results were observed (see table 3.5.6). In unadjusted and adjusted models exposure to electromagnetic fields was not associated with a risk of developing glioma. For unadjusted odd ratios the results were Q2: OR 1.03, 95% CI 0.77-1.37, p-value 0.865 – Q2: OR 1.11, 95% CI 0.84-1.48, p-value 0.463 and Q4: OR 1.10, 95% CI 0.83-1.46, p-value 0.463). For adjusted odd ratios the results were for the 2nd quartile Q2: OR 1.03, 95% CI 0.74-1.42, p-value 0.868 – for the 3rd quartile Q3: OR 1.07, 95% CI 0.76-1.51, p-value 0.685 and for the 4th quartile Q4: OR 1.04, 95% CI 0.73-1.48, p-value 0.835. A non-statistically significant p for trend across the quartiles (p-trend 0.81) shows no risk across the quartiles (see table 3.5.6).

3.5.6 Total EMF exposure classified by SOC codes and risk of developing gliomas

EMF exposure	Control (n=1085)	Case (n=582)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	137	1.00		1.00	
Q2	272	141	1.03 (0.77-1.37)	0.865	1.03 (0.74-1.42)	0.868
Q3	272	153	1.11 (0.84-1.48)	0.463	1.07 (0.76-1.51)	0.685
Q4	272	151	1.10 (0.83-1.46)	0.521	1.04 (0.73-1.48)	0.835
p-trend						0.81

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Similar results were obtained with meningiomas and their association with exposure to electromagnetic fields by occupation (by SOC) (see table 3.5.7). No association was observed between electromagnetic field exposure and the risk of developing meningiomas. The unadjusted crude odd ratios were for the 2nd quartile Q2: OR 0.83, 95% CI 0.56-1.23, p-value 0.357, for the 3rd quartile Q3: OR 0.95, 95% CI 0.65-1.40, p-value 0.798 and for the 4th quartile Q4: OR 0.91, 95% CI 0.61-1.34, p-value 0.617. The adjusted odd ratios were for the 2nd quartile Q2: OR 0.75, 95 % CI 0.49-1.15, p-value 0.182, for the 3rd quartile Q3: OR 0.91, 955 CI 0.58-1.14, p-value 0.662 and for the 4th quartile Q4: OR 0.85, 95% CI 0.54-1.34, p-value 0.491. The odd ratios were not statistically significant for unadjusted and adjusted model, as well as the p for trend (p-trend 0.713) (see table 3.5.7).

3.5.7 Total EMF exposure classified by SOC codes and risk of developing meningiomas

EMF exposure	Control (n=1085)	Case (n=244)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	66	1.00		1.00	
Q2	272	55	0.83 (0.56-1.23)	0.357	0.75 (0.49-1.15)	0.182
Q3	272	63	0.95 (0.65-1.40)	0.798	0.91 (0.58-1.41)	0.662
Q4	272	60	0.91 (0.61-1.34)	0.617	0.85 (0.54-1.34)	0.491
p-trend						0.713

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

With acoustic neuromas, the significant risk reductions were observed in the 2nd and 3rd quartile for both unadjusted and when adjusted for confounding factors (Q2: crude OR 0.56, 95% CI 0.34-0.91, adjusted OR 0.53, 95% CI 0.31-0.90, Q3: crude OR 0.50, 95% CI 0.30-0.83, adjusted OR 0.52, 95% CI 0.29-0.93). In the 4th quartile risk reductions were observed too for both unadjusted and adjusted model, but they were not statistically significant (Q4: crude OR 0.64, 95% CI 0.40-1.03, p-value 0.063 – adjusted OR 0.72, 95% CI 0.41-1.28, p-value 0.263). Nevertheless, there was no clear trend of risk reduction (p for trend 0.287) (see table 3.5.8).

3.5.8 Total EMF exposure classified by SOC codes and risk of developing acoustic neuroma

EMF exposure	Control (n=1085)	Case (n=135)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)†	p-value
Q1	271	50	1.00		1.00	
Q2	272	28	0.56 (0.34-0.91)	0.020	0.53 (0.31-0.90)	0.018
Q3	272	25	0.50 (0.30-0.83)	0.007	0.52 (0.29-0.93)	0.026
Q4	272	32	0.64 (0.40-1.03)	0.063	0.72 (0.41-1.28)	0.263
p-trend						0.287

† Adjusted for age (in 5-year groups), sex, study region, deprivation category (Townsend score reflecting social status)

Overall, a modest statistically significant decreased risk was observed in the 3rd and 4th quartile for adjusted model results for electromagnetic fields exposure by industry (by SIC) and the risk of brain tumours (Q3: OR 0.73, 95% CI 0.55-0.97 and Q4: OR 0.70, 95% CI 0.52-0.94). There was evidence of risk decreasing across all quartiles (p for trend 0.019). Similar results were observed for adjusted odd ratios for electromagnetic fields exposure by industry and the risk to develop gliomas (Q3: OR 0.72, 95% CI 0.51-1.01 and Q4: OR 0.71, 95% CI 0.45-1.00). A clear trend of risk reduction across quartiles was obtained (p for trend 0.03). No association was found between exposure to electromagnetic fields (by SIC) and meningiomas. For acoustic neuromas, even though the unadjusted model showed the inverse associations in the 3rd and 4th quartile (Q3: OR 0.55, 95% CI 0.33-0.92 and Q4: OR 0.59, 95% CI 0.36-0.98), the effects disappeared when adjusted for confounding factors.

No statistically significant associations were found between exposure to electromagnetic fields by Standard Occupational classification (SOC) coding and brain tumours. Also there was no evidence of risk across quartiles (p-trend 0.70). Similar results also obtained with gliomas and meningiomas. With acoustic neuromas, the significant risk reductions were observed in the 2nd and 3rd quartile for both unadjusted and when adjusted for confounding factors (Q2: crude OR 0.56, 95% CI 0.34-0.91, adjusted OR 0.53, 95% CI 0.31-0.90, Q3: crude OR 0.50, 95% CI 0.30-0.83, adjusted OR 0.52, 95% CI 0.29-0.93). Nevertheless, there was no clear trend of risk reduction (p for trend 0.287).

Chapter 4

Discussion

4. Discussion for results on occupational electromagnetic field exposure and the risk of developing brain tumours

Summary of findings

This study is a multi-centre large case-control study which aims to address the effect of low frequency electromagnetic fields (LFEMF) on brain tumours. It presents the results for all brain tumour cases as well as a break down by subtype; gliomas, meningiomas, and acoustic neuromas and their association with cumulative exposure to electromagnetic fields estimated either by Standard Industry Classification (SIC) or by Standard Occupational Classification (SOC) codes. The findings suggest that cumulative exposure according to the Standard Industry Classification (SIC) is inversely associated with all cases of brain tumour. The significant risk reductions were observed in the 3rd and 4th quartile compared to the 1st quartile (approximately by 30% risk reduction). There is evidence of a decrease in risk across quartiles (p for trend 0.019). Similar results were seen with gliomas (p for trend 0.03). For meningiomas and acoustic neuromas, none of the results were statistically significant. On the contrary, on analysis of cumulative EMF exposure by the Standard Occupational Classification (SOC), the protective effects were observed in the 2nd and 3rd quartile for the acoustic neuroma group only (risk reduction of 50%). There was, however, no clear trend of risk reduction for all quartiles.

Comparison with other literature

The study findings were not in keeping with most of the previous literature. There are studies suggesting association between electromagnetic fields exposure and brain tumours and some others reported no association. But there is no evidence that electromagnetic field exposure plays a protective role in adults' brain tumours.

Comparison with studies of similar exposure

As we have mentioned above, limited data exist regarding association between occupational exposure to electromagnetic fields and brain tumours. All previous studies were looking at specific exposure to electromagnetic fields, especially among electric occupations, rather than lifetime exposure to electromagnetic fields. Therefore there is no evidence of lifetime occupational exposure to electromagnetic fields and the risk of having brain tumour.

Comparison with case-cohort and cohort-mortality studies

There are four studies supporting that electromagnetic fields exposure might play a role in the development of brain tumours. In a case-cohort study (145 cases/800 controls, 0.6% of the cohort-workers of electric power companies in the US) assessed magnetic field exposure with the risk of brain tumours an augmented risk was obtained (risk ratio for average exposure: RR 2.5, 95% CI 1.0-6.3, risk ratio for cumulative exposure: RR 1.8, 95% CI 0.7-4.7) (Savitz et al 2000). A refined magnetic field job-exposure matrix was used to estimate the exposure in this study. A cohort mortality study of 138,905 workers of 5 large electric power companies in the US reported a brain tumour mortality rate ratio of 2.6 in the highest exposure category and an increased risk of developing the disease (by 1.94 per microtesla-year of magnetic field exposure) (Savitz & Loomis 1995). In this study, the exposure was estimated by linking individual work histories to data from 2,842 work shift magnetic measurements and death rates analysed with Poisson regression. Theriault et al in a cohort-case study (60 brain tumours cases out of 223,200 employees) found that workers with exposure in the 90th percentile of cumulative exposure > 15.7 microtesla (μT)-years have a non-significant increase risk to develop brain tumours (OR 1.95, 95% CI 0.76-5.00), but there was no elevated risk for glioblastomas (Theriault et al 1994). Estimation of cumulative

exposure for this study was obtained from measurements of 2,066 workers performing tasks similar to those in cohorts using personal dosimeters. The strongest risks were shown in Preston-Martin et al study investigating exposure to electromagnetic fields and the risk of brain tumours among electricians (OR 4.6, 95% CI 1.7-2.2) and electrical engineers (OR 8.2, 95% CI 20-34.7)(Preston-Martin et al 1993). This study uses completely different methods, as it's investigating the pattern of occurrence of brain tumours (5, 684 cases) by occupation and there are no measurements or calculation of electromagnetic field exposure. Only the cohort-mortality study (83,997 employees of the former Central Electricity Generating Board of England and Wales) by Sorahan (2001), showed a highly significant negative trend of risk decreasing with increasing EMF exposure ($p < 0.001$), although most point estimates of risk were close to unity (Sorahan et al 2001). This study used computerized work histories for 79,972 subjects and a detailed calculation of the exposure was performed by others. All these studies showing that exposure to electromagnetic fields might be associated with brain tumours have different sample size compared to our study. The small number of cases compared to the controls that these studies have reduces the power of the evidence. Most of the previous studies assessed exposure based on one high exposed job title, particularly among electric workers. In this study all possible jobs were taken into account. Most of these studies used only measurements obtained with personal dosimeters for the estimation of the exposure and there was no estimation of the exposure by SIC or SOC codes.

In some of the studies no associations were observed (Johansen and Olsen 1998, Harrington et al 1997, Sorahan et al 2001, Johansen and Olsen 2007). In the Johansen and Olsen (1998) cohort study (32 006 workers/ 57 men cases and 15 women cases observed) the results do not support an association (non-significant standard incidence ratio 0.8 (95% CI 0.6-1.0) for men and 1.3 (95% CI 0.7- 2.2) for women) (Johansen and Olsen 1998). Similar results obtained by another cohort

study. A non-significant standard incidence ratio 0.7 (95% CI 0.4-1.3) observed for men and a statistically significant increase standard incidence ratio 1.4 (95% CI 0.5- 3.7) for women, but could not support the hypothesis as the number of women cases observed in cohort was very small (Johansen and Olsen 2007). From a mortality-cohort study of 84,018 male and female employees of Central Electricity Generating Board no association was observed neither between subjects with lower exposures to magnetic fields (0.0-5.3 microT.y) nor between subjects with higher exposures (> or = 13.5 microT.y). The risk of mortality was respectively 1.04 (95% CI 0.60- 1.80) and 0.95 (95% CI 0.54 - 1.69) and there was no evidence of increase trend for cumulative exposure and the risk of mortality for brain tumours (Harrington et al 1997). Comparing these studies with our study, the sample size of the cases is very small compared to the controls and no hypothesis can be supported. The two cohort studies by Johansen and Olsen used only occupational exposure matrix (no individual measurements) for obtaining the electromagnetic field exposure, therefore the estimation of the exposure might not be accurate.

Comparison with case-control studies

The study findings are not in keeping as well with results of previous case-control studies. Three case-control studies reported increase risk between electromagnetic fields exposure and brain tumours. A case-control study (261 cases-1211 controls) conducted in Sweden suggests a relative small increase risk of all brain tumours. The risk estimates were 1.0 (95% CI = 0.7-1.6); 1.5 (95% CI = 1.0-2.2); 1.4 (95% CI = 0.9-2.1) respectively for three consecutive levels of occupational exposure to low-frequency electromagnetic fields (Floderus et al 1993). Estimation of the exposure was based on measurements from 1,015 different workplaces among electric workers. The sample size of cases compared to the controls in Floderus et al study is not big enough and this fact reduces the power of evidence.

Also, the assessment of the exposure is based on a high exposure job title, electric workers, compared to our study where all possible jobs were taken into account.
A case-control study (84 gliomas, 20 meningiomas and 155 controls) reported an increase risk for meningiomas when analysis was based on “electrical occupations” (Relative risk 1.8, 95% CI: 0.3-3.6) and an increase risk for gliomas when analysis based on exposure measurements (Relative risk 1.9, 95% CI: 0.8-5.0) (Rodvall et al 1998). These results do not have strong power as the sample size, especially for meningiomas, is very small. The methodology used in this study is similar to the one of our study, as occupation questionnaires and individual measurements were taken into account for the calculation of the exposure. Also, the assessment of the exposure was based on all possible jobs. Nevertheless, there was no separate evaluation of exposure by SIC or SOC codes.

A population-based case-control study (543 cases-543 controls) investigated the relation between occupational exposure to magnetic fields and brain tumours in men (Villeneuve et al 2002). Even though an increase risk observed for participants who had ever worked in a job with an exposure > 0.6 microT (OR = 1.33, 95% CI: 0.75-2.36) the results were not statistically significant, but a statistically significant augmented risk obtained among glioblastomas cases (OR = 5.36, 95% CI: 1.16-24.78). The sample size of cases and controls is big enough to provide sufficient power for this study. Nevertheless, the exposure was not assigned in this study using occupational coding, as we did in our study. An exposure value based on a time-weighted average (TWA) was used for the estimation, compared to the geometric means we used for the calculation of the exposure. This study took into account all job titles as we did in our study but there was no estimation of exposure by SIC or SOC codes separately.

In a recent case-control study (414 cases-421 controls) Karipidis et al found elevated but non-significant risks for all gliomas (OR 1.4, 95% CI: 0.85-2.27) and

for high grade gliomas (OR 1.51, 95% CI: 0.90-2.53) when low frequency occupational exposure to magnetic fields was assessed with an expert hygienist (Karipidis et al 2007). On the other hand, Karipidis et al study reported inverse association between low and high grade gliomas and exposures assessed by self-report and job exposure matrix (JEM). In addition, another case-control study (454 cases – 908 controls) showed an inverse relation risk between occupational exposure to 50 Hz and brain tumours (RR 0.6, 95% CI 0.3-0.9), but these results were not supported with a statistically significant p-value (Klaeboe et al 2005). These two studies are the only ones that obtained non-significant decreased risks of brain tumours when the electromagnetic field exposure was increasing, even though their results do not support a role of occupational electromagnetic field exposure in the development of brain tumours. These studies have sufficient power of results as they investigate a big size sample and they follow similar methods with our study (job exposure matrix). None of these two studies calculate the exposure by SIC and SOC codes separately.

Overall summary

Overall, the evidence that occupational exposure to electromagnetic fields plays a role in the development of brain tumours is weak. Even though, some existing data indicate an association between electromagnetic field exposure and the disease, it is not yet clear enough whether electromagnetic field exposure is a potential risk factor for brain tumours. The findings of the study are not in common with most of the results observed from previous investigations. Only two case-control studies reported that exposure to electromagnetic fields cause a decreased risk for brain tumours, but the results are not statistically significant and do not support any association (Klaeboe et al 2005, Karipidis et al 2007).

Strengths and Limitations of the study

This study is one of the biggest case-control studies conducted. The total number of 2067 subjects (970 cases and 1097 controls) that was included in the statistical analysis (gliomas n=588; meningiomas n=247; acoustic neuromas n=135; controls=1097) allow us to produce robust evidence of risk, based on statistically significant results. The case response for this study was very high for a cancer case-control study (63% for gliomas, 81% for meningiomas and 89% for acoustic neuromas), and therefore the case sample was representative and unbiased. This study suffers from low participation of controls (44%). This is very common for many population-based case-control studies. Due to ethical constraints, controls were approached and recruited through their general practices. This procedure limited the disclosure of the non-response rate, as it is very likely that a number of non-responders have never been contacted.

It has been suggested that controls taking part in studies tend to be more affluent than non-interviewed controls (Hepworth et al., 2006b). A higher proportion of controls (29.8%) were categorised in the most affluent Townsend core compared to cases (26.9%), particularly for meningiomas (24.7%) and acoustic neuromas (24,4%) and their health consciences may differ from that of the general population (Liu et al., 2001). However, it is unlikely to cause any bias in results.

Confounders such as age in 5-year group, sex, study region and deprivation category based on Townsend score (n=5) (Townsend 1987) were adjusted for in our analysis. Exposure to pesticides and solvents might be a confounder too, but it was not adjusted for in the analysis as we did not have data for this exposure.

In epidemiological studies investigating exposure to electromagnetic fields as a risk factor of brain tumours the major difficulty is to obtain an accurate exposure to

electromagnetic fields (EMF). This difficulty calculating the exposure is due to the fact that we have not indentified a specific method to estimate the accurate exposure to electromagnetic fields. Exposure to electromagnetic fields is complex, as it is generated from several sources, and still it is not found an established methodology to add-up these exposures in one total exposure (Ahlbom et al 2001, WHO –World Health Organization 2007). In addition, difficulties arise for the definition of the induction period to electromagnetic fields (Ahlbom et al 2001). All these are obstacles to establish relevant parameters for the quantification of the exposure to electromagnetic fields and make more difficult the assessment of the effects of this exposure to brain tumours (Ahlbom et al 2001, WHO –World Health Organization 2007).

In our study we used the method of occupational calendars with job titles for the collection of data. This method has the advantage of being based on information relatively easy to obtain, in that it is possible to use secondary data, in addition to being a simple manner to communicate the study's results (Ahlbom et al 2001). There is also a substantial disadvantage to job titles. There is no strong relation between the job title and the workplace electromagnetic field (EMF) exposure (Kelsh et al 2000). Some jobs might seem to be related with high exposure to electromagnetic fields but actually does not produce such exposure, for example the case of line engineers who work most of their time in the office, away from electric facilities (Floderus 1996, Floderus et al 1996). This might be a reason for not finding any association between exposure to electromagnetic fields and brain tumours, as people who weren't actually exposed to electromagnetic fields (EMF) were classified in jobs related with high exposure.

A misclassification might occur by using Standard Industry Classification (SIC) and Standard Occupational Classification (SOC) codes for the calculation of electromagnetic field exposure. Both the Standard Industry Classification (SIC) and

Standard Occupational Classification (SOC) were very broad and would include workers from a wide range of workplaces, thus electromagnetic field (EMF) exposure might not reflect the true exposure. The SIC code system is used for classifying business activities in the UK, and it correlates to and is developed in conjunction with the equivalent European Union's industrial classification system, NACE. NACE stands for Nomenclature Générale des Activités Économiques dans les Communautés Européennes. This is French for Statistical Classification of Economic Activities in the European Community. NACE is a lot easier.SIC codes list has 17 sections and 62 divisions. The SOC code system has two main concepts of classification, kind of work performed - job, and the competent performance of the tasks and duties – skill. The SOC code system has 9 major groups, 25 sub major groups, 81 minor groups and 353 unit groups. Therefore the SOC code system is more specific, rather the SIC code system which is more general. It might be due to this fact that we see such a difference in the results between exposures to electromagnetic fields by SIC codes and by SOC codes. The use of UK SOC list, US SOC list and ISCO88 (a list matching the soc codes for USA and UK), as we mentioned in the methodology section, to obtain geometric means of exposure for the missing SOC codes it is possible to has resulted in bias of our electromagnetic field exposure estimation. Further analysis should be performed using a job exposure matrix (a cross tabulation table where rows contain job titles (they can be extended into more specifically both administrative units and work locations) and columns contain exposure indices. Such matrixes comprised algorithms of lesser or higher complexity that may take into account job title, workplace, description of activities developed, utilization of electric equipment, and even MF measured by personal dosimeters in a sample of workers. The putative aetiological time window period prior to diagnosis should also be taken into account (Ahlbom et al 2001).

The healthy worker effect is often observed in occupational studies of which working populations have a lower overall death rate than the general population, and also ill and disabled people are excluded from employment (Li & Sung, 1999). It was first described by William Ogle (Ogle, 1885), who observed that the working population is healthier than the general population. In our study population, the healthy worker effect (HWE) could potentially be a source of selection bias (Li & Sung, 1999; McMichael, 1976). Healthy individuals gain employment and remain in industry. It is likely that ill or disabled people are excluded from employment or do not remain employed (Bakirci et al., 2006). The speculation that workers in industries with high exposures are fitter than people remaining in other jobs was mentioned by Sorahan and colleagues (Sorahan et al., 2001). Some cases that were seriously ill either did not want to participate or were excluded from the study, this could have affected the cumulative exposure level in our case group.

Summary of discussion

Overall, the study findings suggest no evidence of an increased risk for brain cancer with electromagnetic field (EMF) exposure. The fact that people in employment are likely to be fit and healthy (the healthy worker effect) could introduce selection bias and therefore these results should be interpreted with caution. We also have to consider the difficulty to estimate the true exposure to electromagnetic fields. Both the SIC and SOC classification include workers from a wide range of workplaces, thus electromagnetic field (EMF) exposure might not reflect the true exposure. The fact that there is no strong relation between the job title and the workplace electromagnetic field (EMF) exposure should also be taken into account. Some jobs might seem to be related with high exposure to electromagnetic fields but actually does not produce such exposure.

Chapter 5

Conclusion

5. Conclusion for the occupational electromagnetic field exposure and the risk of brain tumours

This study is a large population based case-control study. It aimed to investigate the role of electromagnetic fields (EMF) and risk of developing brain tumours including its subtypes such as gliomas, meningiomas and acoustic neuromas. Individual occupational EMF exposure was calculated for all held jobs by multiply generic electromagnetic field (EMF) geometric means derived from the Standard Industry Classification (SIC) and Standard Occupation Classification (SOC) with time spent on each job. The cumulative exposure was the summation of electromagnetic field (EMF) exposure from all jobs.

The results showed statistically significant risk reductions when EMF exposures were characterised by the SIC Q3: OR 0.73, 95% CI 0.55-0.97 and Q4: OR 0.70, 95% CI 0.52-0.94). There is evidence of a decrease in risk across quartiles (p for trend 0.019). Similar results were observed with gliomas (Q3: OR 0.72, 95% CI 0.51—1.01 and Q4: OR 0.70, 95% CI 0.49-0.99 - p for trend 0.03). For meningiomas and acoustic neuromas, none of the results were statistically significant. On the contrary, on analysis of cumulative EMF exposure by the Standard Occupational Classification (SOC), the protective effects were observed in the 2nd and 3rd quartile for the acoustic neuroma group only (Q2: crude OR 0.56, 95% CI 0.34-0.91, adjusted OR 0.53, 95% CI 0.31-0.90, Q3: crude OR 0.50, 95% CI 0.30-0.83, adjusted OR 0.52, 95% CI 0.29-0.93).There was, however, no clear trend of risk reduction for all quartiles.

These findings suggest no evidence of an increased risk for brain cancer with EMF exposure. The fact that people in employment are likely to be fit and healthy (the healthy worker effect) could introduce selection bias and therefore these results should be interpreted with caution (Li & Sung 1999, McMichael 1976, Bakirci et al

2006, Sorahan et al 2001). We also have to consider the difficulty to estimate the true exposure to electromagnetic fields, as a specific method to estimate the accurate exposure to electromagnetic fields has not been identified (Ahlbom et al 2001). Both the SIC and SOC classification include workers from a wide range of workplaces, thus electromagnetic field (EMF) exposure might not reflect the true exposure. The fact that there is no strong relation between the job title and the workplace electromagnetic field (EMF) exposure should also be taken into account (Kelsh et al 2000). Some jobs might seem to be related with high exposure to electromagnetic fields but actually does not produce such exposure (Floderus 1996, Floderus et al 1996).

The WHO international EMF project has recommended that the design of electromagnetic field (EMF) studies should be such as to include as much information relevant to alternative metrics as possible in order to aid future research (Word Health Organisation, available on http://www.who.int/peh-emf/project). These alternative metrics could be time-weighted average (TWA), geometric mean (GM), intermittency (ITM), maximum measure (MAX), time-weighted average of measurements in harmonic frequency range across the work shift (H-TWA), and percent of time above 0.2 μT across the work shift (%>0.2 μT) (van Tongeren et al 2004). All these metrics can be obtained by specific log-transformations.

Aiming at enhancing a more accurate quantification of occupational exposure we can invest in the development of job-exposure matrixes (JEM). These matrixes have been employed to assign cumulative exposure to workers in several epidemiological studies. The job-exposure matrix (JEM) is a cross tabulation table where rows contain job titles and columns contain exposure indices (Marcílio et al 2009). In order to assign more accurate and precise exposure estimates there is a need these matrixes to comprised complex algorithms that will take into account

specific job title, description of the tasks each worker is performing, workplace, accurate time of working and even direct measurements of exposure with individual dosimeters (Marcílio et al 2009). Therefore, task-based questionnaires should be created, in addition with more detailed occupational calendars, in order to assign all workers within a job the right mean of exposure and avoid misclassification (Benke et al 2000, van Tongeren et al 2004). As direct measurements with individual dosimeters seem to be the preferred mode of assigning accurate exposure estimates, it is recommended data for all subjects in a case-control study to be obtained using this method too (van Tongeren 2004). Any further study being conducted needs to have sufficient power of detecting relative risks, therefore it is necessary to have a big sample size for all cases, also for the specific subtypes of cases (gliomas, meningiomas, acoustic neuromas etc), and for controls (Ahlbom et al 2001). Also, cases with high illness need to be included in our measurements for more precise estimates of the exposure, as sometimes very ill cases refuse or not be able to answer the questionnaire or accept to participate in the direct measurements.

As exposure to pesticides and solvents may be a confounder, it would be better if data for the estimation of this exposure obtained, with the method of occupational calendars, and afterwards this exposure adjusted for in the electromagnetic field (EMF) analysis. In the UK Adults Brain Tumour Study (UKABTS) a rich dataset for exposure to pesticides and solvents is available for further investigations. Adjustment for age, sex, region, and deprivation category is recommended for any further analysis as they are confounders too.

Overall summary of the conclusion

In conclusion, the results from the epidemiological studies investigating the association between electromagnetic fields exposure and brain tumours are

inconsistent. The findings of this study do not support the hypothesis that the risk to develop brain tumour increases with the increase of the electromagnetic field exposure. This study's results reported inverse association between electromagnetic fields exposure and the disease. This is probably due to the healthy worker effect (HWE), misclassification of jobs and difficulties in the estimation of the exposure. Further studies must be carried out, with detailed complex job-exposure matrixes (JEMs), better classification and the need to include cases with high illness, in order to achieve more accurate and precise results.

6. APPENDIX

6.1 Courses, seminars and published journals

Postgraduate training courses attended during the first year (2003-2004 sessions):

- Introduction to Faculty PG Training Programme
- Introduction to Library Skills I
- Introduction to Library Skills II
- Presentation Skills
- Time Management
- Critical Analysis I
- Critical Analysis II

Community Health Science courses attended during the first year (2003-2004):

- Research in epidemiology with basic statistics
- Further Quantitative Methods in Health Service Research

Seminars attended during the first year 2003-2004:

- IARC International Course on Epidemiological research in Nutrition and Cancer, organized by the International Agency for research on Cancer (IARC), in Lyon, France from 8-13 December 2003

Published papers:

- Dietary zinc intake and brain cancer in adults: a case-control study
  British Journal of Nutrition (2008), 99:667-673 Cambridge University Press

- Occupation and exposure to electromagnetic fields and the risk of brain tumours; a UK case control study
  This journal was submitted to American Journals of Epidemiology (AJE) and waits for publication.
- Determinants of occupational exposure to extremely low frequency electromagnetic fields in the general population in the UK. In press. (2007)

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